"A PROSPECTIVE, RANDOMIZED PLACEBO-CONTROLLED STUDY EVALUATING THE EFFECTIVENESS OF ORAL PREGABALIN AND TRAMADOL FOR POSTOPERATIVE PAIN MANAGEMENT IN PATIENTS UNDERGOING LUMBAR LAMINECTOMY"

Dissertation submitted to

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in partial fulfilment for the award of the degree of

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IN

ANAESTHESIOLOGY

BRANCH X

INSTITUTE OF ANAESTHESIOLOGY & CRITICAL CARE
MADRAS MEDICAL COLLEGE
CHENNAI- 600 003

APRIL 2015

CERTIFICATE

This is to certify that the dissertation entitled, **"A PROSPECTIVE, RANDOMIZED PLACEBO-CONTROLLED STUDY EVALUATING THE EFFECTIVENESS OF ORAL PREGABALIN AND TRAMADOL FOR POSTOPERATIVE PAIN MANAGEMENT IN PATIENTS UNDERGOING LUMBAR LAMINECTOMY"** submitted by **Dr.V.REENA SANGES**, in partial fulfilment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamilnadu Dr. M.G.R. Medical University, Chennai., is a bonafide record of the work done by her in the INSTITUTE OF ANAESTHESIOLOGY & CRITICAL CARE, Madras Medical College and government hospital, during the academic year 2012-2015.

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DECLARATION

I hereby, solemnly declare that this dissertation entitled **"A PROSPECTIVE, RANDOMISED PLACEBO-CONTROLLED STUDY EVALUATING THE EFFECTIVENESS OF ORAL PREGABALIN AND TRAMADOL FOR POSTOPERATIVE PAIN MANAGEMENT IN PATIENTS UNDERGOING LUMBAR LAMINECTOMY"** is a bonafide work done by me in the Institute of Anaesthesiology and Critical Care, Madras Medical College and Government General hospital, Chennai, during the period 2012 to 2015 under the guidance of **Prof. Dr.B.KALA M.D.,D.A.,** Director, Institute of Anaesthesiology and Critical Care, Madras Medical College and Government General Hospital, Chennai – 3 and submitted to **The Tamilnadu Dr. MGR Medical University,** Guindy, Chennai – 32, in the partial fulfilment of the requirements for the award of the degree of MD Anaesthesiology (Branch X), examinations to be held on April 2015.

I have not submitted this dissertation previously to any university for the award of degree or diploma.

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CONTENTS

A PROSPECTIVE, RANDOMIZED, PLACEO-CONTROLLED STUDY EVALUATING THE EFFECTIVENESS OF ORAL PREGABALIN AND TRAMADOL FOR POSTOPERATIVE PAIN MANAGEMENT IN PATIENTS UNDERGOING LUMBAR LAMINECTOMY

ABSTRACT:

Postoperative pain is one of the most feared problems among patients coming for surgery. Preventing and treating postoperative pain is a big deal despite recent advances in pain therapy. Opioids continue to be a cornerstone in the treatment of postoperative pain inspite of their side effects. Pregabalin, a structural analog of gamma-aminobutyric acid, has been used for the treatment of neuropathic pain and as an adjuvant in treating partial seizures. This study was thus taken up to compare the analgesic and anxiolytic effects of pregabalin and tramadol by administering it preoperatively in patients undergoing elective decompressive lumbar laminectomy. The study was conducted in 75 patients belonging to ASA 1 & 2 between 20 to 60 years. These patients were randomly allocated into three groups- group 1, 2 & 3 containing 25 patients each. Group 1, 2 & 3 received placebo capsule, 100mg tramadol capsule and 150 mg pregabalin capsule respectively 1 hour before

anaesthetic induction. Pregabalin showed stastistically significant analgesic and anxiolytic effect when compared to placebo but less than that of tramadol. Also, pregabalin was associated with less sedation than that of tramadol. Postoperative complications like nausea, vomiting, drowsiness was less in pregabalin group compared to placebo group. Also, pregabalin provided a stable hemodynamics throughout the intraoperative period and also prevented the pressor response to laryngoscopy and intubation similar to tramadol. The result of this study support the use of pregabalin for postoperative pain relief as it has fewer side effects, well tolerated and higher patient satisfaction.

KEYWORDS:

Pregabalin , Tramadol, postoperative pain, lumbar laminectomy.

INTRODUCTION

Postoperative pain is one of the most feared problems among patients coming for surgery.

Postoperative pain management includes pain management[22], prevention and treatment of postoperative complications[90] and restoring preoperative function[16].

Preventing pain and treating it is a big deal despite significant advancements in pain assessment and therapy[2]. By mobilising patients at the earliest, postoperative complications are reduced. It has been reported that roughly 80% of patients undergoing surgical procedures experience postoperative pain[2]. Pain on movement is comparatively resistant to opioids than the pain during rest[91] and can lead to postoperative pulmonary[49], cardiac[33], and thromboembolic complications[63, 56, 15].

The guidelines for postoperative pain treatment has been revised and drugs like S-ketamine, pregabalin, metamizole, oxycodone are used as new methods of preventing postoperative pain.[45]

Prolonged chronic pain after surgery has been under recognised until recently which is actually a very common phenomenon.

A number of risk factors and predictors including the age, gender, surgical procedure, pre and postoperative pain, genes, psychosocial factors and pain modulation variables have been identified.

Together with an increased knowledge about the pathophysiology of chronic pain after surgery it may be possible to develop successful drugs and interventions in the near future.

Post-surgical pain is normally perceived as nociceptive pain. Surgical trauma causes central and peripheral sensitization and hyperalgesia which when untreated can lead to chronic postoperative pain after surgery.

Indeed pain is one among the three most common causes of delayed discharge after ambulatory surgery next to drowsiness and nausea/vomiting.

Antihyperalgesic drugs improve the postoperative pain by preventing the development of central sensitisation.[99]

The recent advance in postoperative pain management includes finding out the exact mechanism of action of drugs at molecular level, newer routes and modes of analgesic delivery.

For years opioids have been the cornerstone of postoperative pain management inspite of their side effects. Hence the search for newer analgesics and combination of analgesics and other non-opioid drugs

continues in order to improve postoperative analgesia and reduce opioid related side effects.[3]

In this context, the gabapentinoids (gabapentin and pregabalin) have been extensively studied.

Gabapentinoids were successfully used in the treatment of trigeminal neuralgia, diabetic neuropathy, post herpetic neuralgia[46, 14, 57, 77, 51, 18]. In addition their usefulness for postoperative pain relief is also studied[55, 7]

The present study was thus taken up to test the efficacy of pregabalin for pain management in lumbar laminectomy.

AIMS AND OBJECTIVES

AIM:

The aim of my study is to assess and compare the efficacy and safety of preoperative administration of pregabalin and tramadol in patients undergoing elective lumbar laminectomy.

OBJECTIVES:

To measure the analgesic, anxiolytic and sedative effects by VAS score, anxiety score and Ramsay sedation score respectively.

To evaluate the intraoperative hemodynamics.

To assess their adverse effects.

PAIN PATHWAYS AND THE NEUROBIOLOGY OF NOCICEPTION

The physiological processes involved in nociception are

1. Transduction- process by which a noxious stimuli produced by tissue injury gets converted into electrical signals. It occurs in nociceptors (Free endings of Aδ and C fibres).

2. Transmission – process of pain impulse transmission by the nociceptors from periphery to the spinal cord and then to thalamus and finally to the cerebral cortex. Aδ and C fibres, spinothalamic and spinoreticular tracts are involved in this.

3. Modulation- process by which pain impulses produced are either inhibited or facilitated. It occurs peripherally in nociceptors and also in dorsal horn of the spinal cord and supraspinal structures.

4. Perception – process by which pain produces conscious multidimensional experience. Areas of cortex involved are the reticular system, somatosensory cortex and the limbic system.

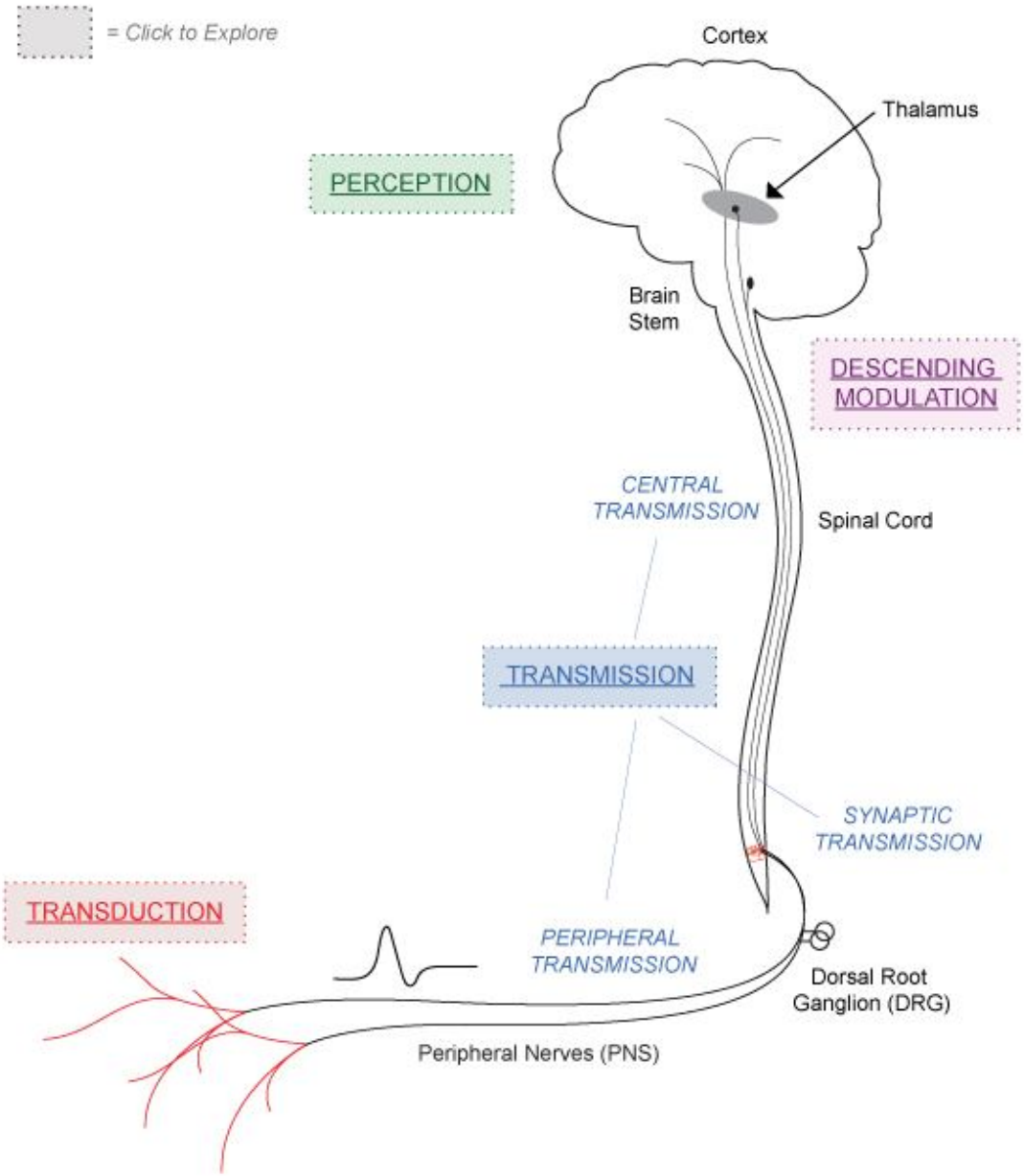

Figure 3.1 Pain pathway and physiology

Surgery produces tissue injury which results in release of histamine and inflammatory mediators such as peptides (e.g., bradykinin), lipids (e.g., prostaglandins), neurotransmitters (e.g., serotonin), and neurotrophins (e.g., nerve growth factor)[51]. This activates the peripheral nociceptors, which initiate transduction and transmission of nociceptive information to the central nervous system (CNS) as well as the process of neurogenic inflammation in which release of neurotransmitters (substance P and calcitonin gene–related peptide) in the periphery causes vasodilatation and plasma extravasation.[51] Noxious stimuli are transduced by peripheral nociceptors and then transmitted by Aδ and C nerve fibres from peripheral somatic and visceral sites to the dorsal horn of the spinal cord, where integration of peripheral nociceptive and descending modulatory input (i.e., norepinephrine, serotonin, encephalin, γ-aminobutyric acid) occurs. Further transmission is determined by complex modulating influences in the spinal cord. Some impulses pass to the ventral and ventrolateral horns which initiate segmental (spinal) reflex responses, that may be associated with inhibition of phrenic nerve function, increased skeletal muscle tone, or even decreased gastrointestinal motility while others are transmitted to higher centres through the spinoreticular and spinothalamic tracts where they induce cortical and suprasegmental responses to ultimately produce the perception of and affective component of pain. Continuous release of inflammatory mediators in the periphery causes sensitization of

functional nociceptors and activates dormant ones.[18] Sensitization of peripheral nociceptors leads to decreased threshold for activation, increased rate of basal (spontaneous) discharge and increased rate of discharge with activation.[18] It may also result in central sensitization ("persistent postinjury changes in the CNS that result in pain hypersensitivity")[55] and hyperexcitability ("exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage").[55] Such noxious input may cause functional changes in the dorsal horn of the spinal cord which may later on cause postoperative pain to be perceived as more painful than it would have been. Thus the neural circuitry in the dorsal horn is extremely complex.

However, it seems that certain receptors (e.g., N-methyl-d-aspartate [NMDA]) may be especially important and the second messenger effectors (e.g., substance P, protein kinase C) may also play important roles in spinal cord sensitization and development of chronic pain after acute pain.[7] Thus from the hard- wired system proposed by Descartes in the 17th century our current understanding of neurobiology of nociception has travelled to a new dimension of neuroplasticity in which modulation and dynamic integration of nociceptive transmission take place at several levels. Still our knowledge is deficit regarding the specific roles of various neurotransmitters, receptors, and molecular structures in the process of nociception.

The traditional dichotomy between acute and chronic pain is arbitrary and studies demonstrate that transition is quick from acute to chronic pain.[18] Experimental studies show that noxious stimuli can produce expression of new genes (which forms the basis of neuronal sensitization[7]) in the dorsal horn of the spinal cord within 1 hour and which are sufficient enough to alter behaviour within the same duration.[9] Clinical studies also suggest that the intensity of acute postoperative pain is a significant predictor of chronic postoperative pain.[71] Thus preventive analgesia and multimodal analgesia may be important in facilitating short as well as long-term patient convalescence after surgery.

ACUTE AND CHRONIC EFFECTS OF POSTOPERATIVE PAIN

ACUTE EFFECTS[58, 113, 25]

Emotional and physical suffering

Sleep disturbance

Cardiovascular system: tachycardia, hypertension, increased oxygen consumption, myocardial ischemia, deep venous thrombosis

Respiratory system: decreases lung volumes, impairs cough, sputum retention, infection, atelectasis

Gastrointestinal system: reduces bowel motility

Genitourinary system: urinary retention

Central nervous system: anxiety

Endocrine system: increases catabolic hormones, increases blood glucose, causes sodium and water retention

Immunological impairment, infection, delayed wound healing.

Control of acute postoperative pain may attenuate the sympathetic outflow, stress response, inhibitory spinal reflexes and contribute to improvements in patient morbidity, mortality and outcomes (health- related quality of life [HRQL], patient satisfaction).

CHRONIC EFFECTS:

Risk of development of chronic pain

Risk of behavioural changes especially in children

Delay in long term recovery.

PREVENTIVE ANALGESIA

The concept of pain prevention was first introduced by Crile in 1913[24] and later developed by Wall[96] and Wolf[100].

Central sensitization and hyper excitability develop after surgical incision which results in amplification of postoperative pain.

Preventing the establishment of altered central processing by analgesics may result in short and long term benefits for the patient during convalescence.[16]

DEFINITION:

Definitions of pre-emptive analgesia include what is administered before the surgical incision, what prevents the establishment of central sensitization resulting from incisional injury only(i.e., intraoperative period), what prevents central sensitization resulting from incisional and inflammatory injury(i.e., intraoperative and postoperative periods), or the entire perioperative period encompassing preoperative interventions, intraoperative analgesia, and postoperative pain management(i.e., preventive analgesia).[55]

SCIENTIFIC RATIONALE:

As already discussed above, tissue damage detected by free nerve endings (peripheral nociceptors) are transduced by them and transmitted by Aδ and C fibres to the dorsal horn of spinal cord.

The myelinated Aδ fibres conduct rapid, sharp and well localised pain called the first pain. Unmyelinated C fibres conduct duller, slower and poorly localised pain called the second pain.

The dorsal horn consists of two groups of neurons. Nociceptive specific (NS) neurons respond only to noxious stimuli from Aδ and C fibres. Wide dynamic range (WDR) neurons respond to both noxious stimuli and non- noxious stimuli from Aβ fibres (touch). Activity of WDR neurons depend on excitatory and inhibitory input from nociceptive and non- nociceptive peripheral nerve fibres and descending input from supraspinal sites.

Tissue damage during surgery results in conduction of noxious stimuli from nociceptors to dorsal horn neurons (NS and WDR) which results in altered responsiveness of these neurons.

Stimuli from Aδ and C fibres are amplified (i.e.,) hyperalgesia and stimulus from Aβ fibres are misinterpreted (i.e.,) allodynia. This is central sensitization.

Pre-emptive analgesia may help to prevent the neurological and biochemical consequences of noxious input to central nervous system.

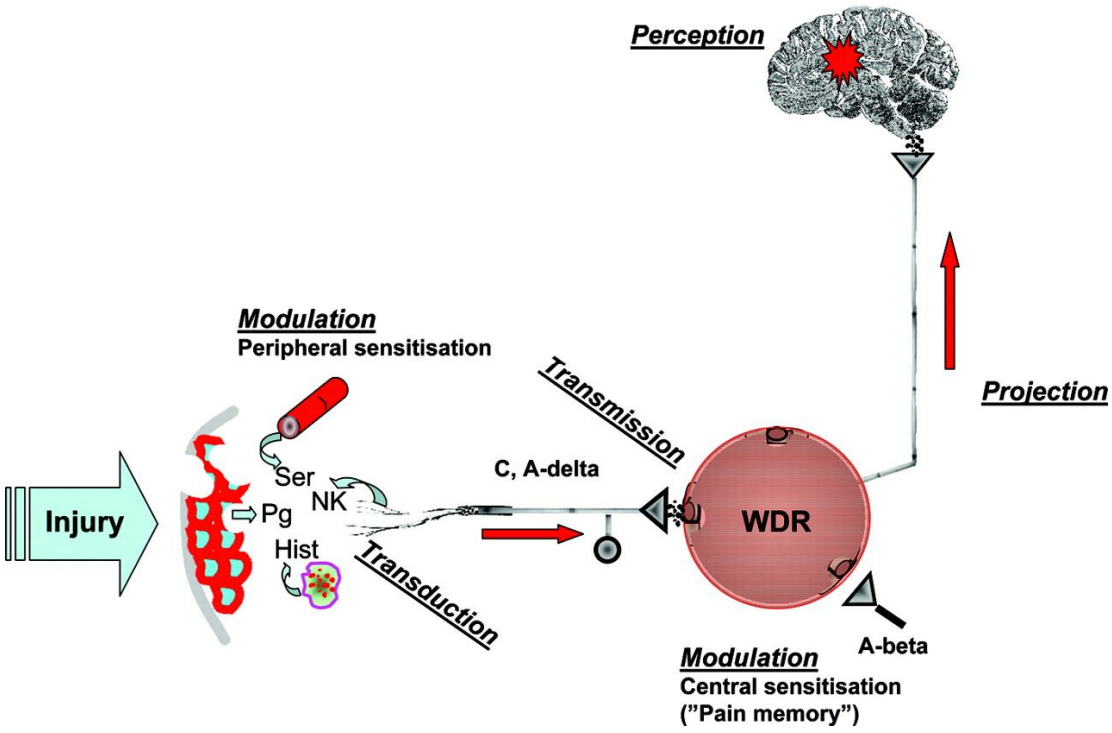

Figure 4.1 Pathophysiology of pain

MULTIMODAL APPROACH TO PERIOPERATIVE RECOVERY

Kehlet and Dahl were the first to describe the concept of combining multiple analgesic techniques in 1993[72]

By applying multimodal strategy the analgesic benefits of controlling postoperative pain are generally maximised and opioid related adverse effects are reduced.

Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms at different sites in the nervous system such that adequate analgesia is attained with lower doses and reduced incidence of side effects.

To attain maximum benefit pain management must be initiated in the preoperative period, continued intraoperatively and in the postoperative period.

BENEFITS

Effective analgesia due to synergistic action.

It is useful in patients at risk for larger doses of opioids such as elderly, obstructive sleep apnoea and chronic pain patients.

Fewer side effects due to lower dosage of drug used.

Faster recovery.

GABAPENTINOIDS IN PAIN MANAGEMENT

Gabapentinoids (Pregabalin and Gabapentin) were originally introduced as antiepileptic but they also have analgesic, anticonvulsant and anxiolytic effects.

These drugs are easily tolerable and have limited side effects

GABAPENTIN

Gabapentin binds to the α-2 delta subunit of the presynaptic voltage gated calcium channel, inhibits the release of calcium, thereby preventing the release of excitatory neurotransmitters involved in the pain pathways.[3, 44]

Gabapentin has demonstrated the analgesic effect in postherpetic neuralgia, diabetic neuropathy and neuropathic pain.

It produces a significant opioid sparing effect and decreases post-operative pain score relative to control group.[60, 86]

PREGABALIN

Pregabalin is a structural analog of GABA (gamma amino- butyric acid).

Pregabalin acts by presynaptic binding to the α-2λ subunit of the voltage gated calcium channel.

These channels are widely distributed in brain and the spinal cord.[31]

By binding to the calcium channels, pregabalin modulates the release of several excitatory neurotransmitters like norepinephrine, glutamate, substanceP, and calcitonin gene – related peptide.

This leads to inhibitory modulation of "overexcited neurons" and returns them back to their "normal" state.

It also reduces the hyperexcitability of dorsal horn neurons that is induced by tissue damage.[31]

To sum up, pregabalin has a more appropriate pharmacological profile than gabapentin, including dose dependent absorption and far more potent than gabapentin while producing fewer adverse effects[29, 38, 64]

PHARMACOLOGY OF PREGABALIN[30, 8]

Pregabalin belongs to the gabapentenoid group of drugs. It possesses chemical structure similar to inhibitory neurotransmitter GABA (gamma amino butyric acid). Pregabalin has got similar properties like the prototype drug gabapentin.

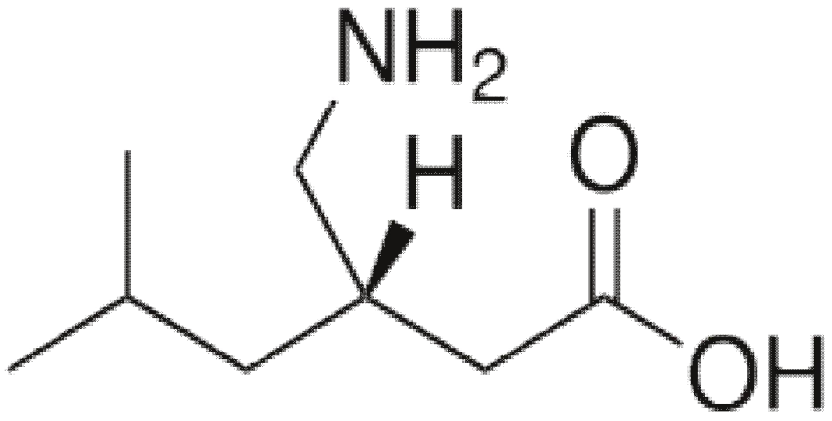

Figure 7.1 Chemical structure of Pregabalin

Pregabalin which is chemically S-(+)-3-isobutylgaba (Fig-7.1), was designed as a lipophilic analogue of GABA (gamma-amino butyric acid) substituted at the 3-position to facilitate diffusion across blood brain barrier. 3-isobutylgaba exists in isomeric forms, rendering the drug pharmacologically active enantiomer.

DRUG APPROVAL[30]

July 2004–European Commission, granted the pharmaceutical company Pfizer, approval for pregabalin for the treatment of peripheral neuropathy and as an adjunctive therapy for partial seizures in patients with epilepsy.

December 2004-The Food and Drug Administration (FDA) approved pregabalin, for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and post herpetic neuralgia.

June 2005-The FDA approved pregabalin for use as an adjuvant in partial seizure treatment.

March 2006- Pregabalin got approval from European commission, for the treatment of generalised anxiety disorder

Pregabalin is placed in Schedule V of the controlled substance act, based on the report of euphoria in controlled clinical trials.

MECHANISM OF ACTION

Pregabalin is only structurally related to the inhibitory neurotransmitter GABA. It neither acts on GABA receptor, nor mimics it physiologically. The precise mode of action of pregabalin has not been fully elucidated. Pregabalin has got similar pharmacological profile as gabapentin. The main site of action of pregabalin is on the alpha 2 delta subunit of neuronal calcium channels.

PREGABALIN- AN ALPHA 2 DELTA LIGAND[17]

Alpha 2 delta is a subunit of presynaptic, voltage-gated calcium channel. The main site of action of pregabalin is this alpha 2 delta subunit of neuronal calcium channels. This binding reduces the depolarisation induced calcium influx at nerve terminals. As a consequence, there is reduction in the release of several excitatory aminoacids like glutamate, noradrenaline, substance-P, and CGRP (Calcitonin Gene Regulated Peptide). This modulation of neurotransmitter release by pregabalin contributes to its anticonvulsant, anxiolytic, and analgesic property.

Voltage gated calcium channels are divided into six types P, Q, N, L, R, and T-type channels. N-type calcium channels are involved in pain sensitization phenomenon in response to noxious stimuli. Calcium channel blockers like nifedipine binds to L-type channels, whereas pregabalin binds to N-type. Cardiac and other peripheral tissues have L-type calcium channels. This explains the lack of cardiovascular side effects with pregabalin.

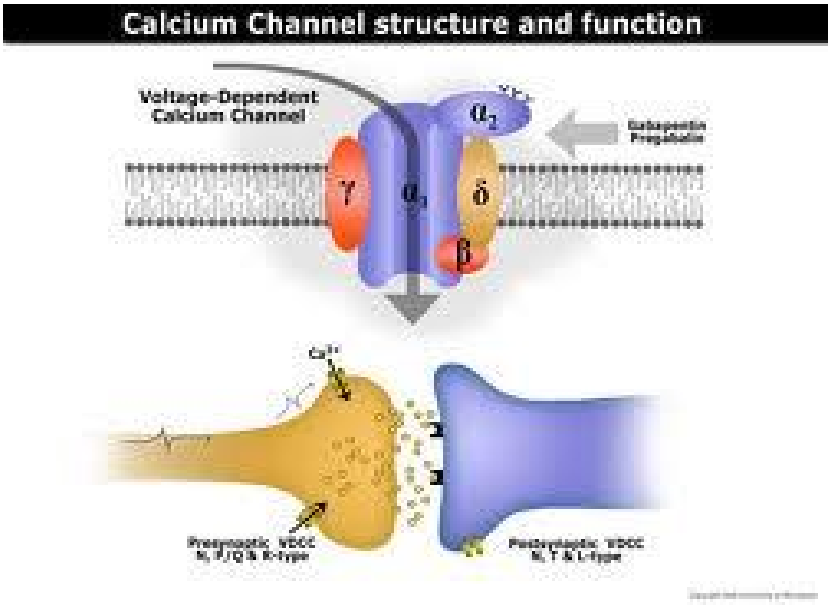

Figure 6.2 Structure of calcium channel

DOSAGE AND ADMINISTRATION

For painful diabetic peripheral neuropathy, the maximum recommended dosage is 100 mg thrice a day. Because pregabalin is eliminated primarily by renal excretion, the dose needs to be reduced in patients with reduced renal function. For peripheral neuropathy, dosing should begin at 75 mg per day, and may be increased to 300 mg per day within a week based on efficacy and tolerability.

PHARMACOKINETICS

Pregabalin has consistent and dose proportionate pharmacokinetics. The mean elimination half-life of pregabalin is 6.3 hours, and is independent of dose and repeated administration. This consistent dose-proportional pharmacokinetics of pregabalin provides confidence in the prediction of dose-response relationship in clinical practice. Administration of pregabalin with food has no effect on its absorption[13].

DISTRIBUTION, METABOLISM, ELIMINATION

L-transporter is an important system which is responsible for the transport of substances across the brain and gut. Pregabalin is a substrate of this system and hence crosses blood brain barrier rapidly. This property is essential for a drug that influences central nervous system activity.

In humans, pregabalin undergoes less than 2% metabolism. It is excreted unchanged by the kidneys. In patients with compromised renal function the dose of pregabalin needs to be reduced. In patients with creatinine clearance between 30 to 60 ml/minute, daily dose of pregabalin needs to be reduced by 50% when compared to patients with creatinine clearance more than 60 ml/minute.

PREGABALIN VERSUS GABAPENTIN

Though pregabalin and gabapentin belongs to same group and possesses similar chemical structure, pregabalin has better pharmacokinetic properties as discussed previously.

Table 7.1 Pharmacological properties of pregabalin[8]

Property	Clinical significance
1. High affinity for α2δ receptor	New mechanism of action
2. No effect on GABA	No retinal or optic nerve toxicity
3. Linear dose proportional Cmax	Predictable level and dose response
4. Lack of protein binding	No drug interactions
5. Negligible metabolism	No drug interactions
6. Renal excretion (98% unchanged)	Dose reduction in renal impairment
	No hepatic effects
7. Rapidly cross blood brain barrier	Access to CNS site of action

Cmax- maximum plasma concentration

PREGABALIN LACKS DRUG - DRUG INTERACTIONS

Pregabalin does not bind to plasma proteins and is not subjected to hepatic metabolism. Studies done on human liver microsomes have demonstrated that pregabalin does not affect the cytochrome P450 system.

These facts indicate that pregabalin is unlikely to cause pharmacokinetic drug interactions. This property is important when administering pregabalin with other anticonvulsant drugs.

SAFETY IMPLICATIONS

Pregabalin does not completely block calcium channel function or transmitter release, even at high concentration. This property could have important safety implications in case of drug overdose. Alpha 2 delta ligands acts on N-type calcium channels, and have little effect on voltage gated calcium channels of heart(L-type), or other peripheral tissues. Hence, pregabalin has no effect on arterial blood pressure or cardiac function at therapeutic doses.

CLINICAL USES

Highly effective adjunctive therapy in the treatment of partial seizures

Chronic pain syndromes like, diabetic peripheral neuropathy, and post herpetic neuralgia.

Chronic anxiety disorder.

Adjuvant in acute pain management.

Since pregabalin possess anticonvulsant, sedative, analgesic, and anti-hyperalgesic properties, studies are being done on potential perioperative uses like pre-operative sedation, anxiolysis, reduced intraoperative opioid requirement, and attenuation of hemodynamic stress response to laryngoscopy and tracheal intubation.

Alpha 2 delta receptor seems to be involved in the phenomenon of neuronal hypersensitisation to noxious stimuli. Blunting of this hypersensitisation by pregabalin helps in reducing the intensity of post-operative pain and has got opioid sparing effect.

SIDE EFFECTS AND PRECAUTIONS

Pregabalin is a well-tolerated, relatively safe drug with dose-dependent adverse effects which are mild to moderate and usually transient.

1. Dizziness (29%)
2. Somnolence (22%)
3. Dryness of mouth (9.1%)
4. Blurred vision (6.4%)
5. Edema (6.1%)
6. Weight gain (5.6%)
7. Abnormal thoughts (5.4%)

There are case reports of myoclonus, gynaecomastia, and a single case report of carpus callosum edema. Withdrawal of pregabalin after long term therapy should be gradual as it may potentiate seizure activity.

Pregabalin is contraindicated in patients with history of allergy to the drug or any of its components. FDA placed pregabalin in class C for pregnant patients. It is not recommended in pregnancy and breast feeding. Dose needs to be reduced in patients with reduced renal function.

PHARMACOLOGY OF TRAMADOL

Tramadol is a centrally acting atypical opioid with additional serotonin-norepinephrine reuptake- inhibitory action.[36]

It is marketed as a racemic mixture of both R- and S- enantiomers as they are known to complement each others analgesic efficacy. It is called an atypical opioid because apart from being a serotonin reuptake inhibitor it is a fairly weak μ-opioid receptor agonist.

CHEMICAL SRUCTURE OF TRAMADOL

(1R, 2R)- tramadol ; (1S, 2S)- tramadol

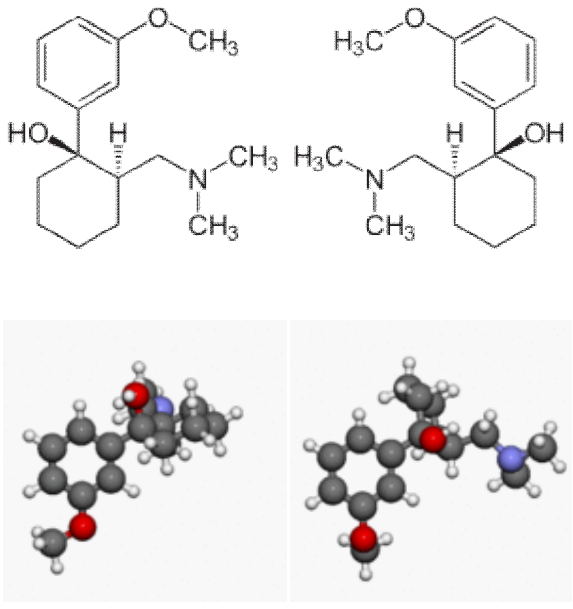

Figure 8.1 Chemical structure of Tramadol

Tramadol is chemically [2-(dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexanol]. Tramadol has two stereogenic centres at the cyclohexane ring. Thus it may exist in four different configurational forms.

(1R,2R)-isomer

(1R,2S)-isomer

(1R,2S)-isomer

(1S,2R)-isomer

DRUG APPROVAL[39-42]

March 1995- FDA approval for treatment of moderate to moderately severe pain.

September 2005- FDA approval for extended release formulation

May 2005- FDA approval of Tramadol for orally disintegrating form for treatment of moderate to moderately severe pain.

August 2014- Tramadol has been placed into schedule IV of the federal Controlled Substances Act.

MECHANISM OF ACTION[42, 30, 26, 39, 66, 79, 59, 80, 78]

Tramadol acts as a μ- opiod receptor agonist, serotonin releasing agent, norepinephrine reuptake inhibitor.

It is also an NMDA receptor antagonist, 5- HT_{2C} receptor antagonist, nicotinic acetyl choline receptor agonist, transient receptor potential cation channel (TRPV1) and M_1 and M_2 muscarinic acetylcholine receptor antagonist.

Tramadol has inhibitory action on 5- HT_{2C} receptor which could be partially responsible for tramadol's reducing effect on depressive and obsessive-compulsive symptoms in patients with pain and comorbid neurological illness. It may also be responsible for its seizure lowering threshold. However, it may also be attributed to tramadol's putative inhibition of $GABA_A$ receptors at high doses.

The metabolite, O- desmethyltramadol, is a high affinity ligand of δ- and κ- opioid receptors and δ- opioid receptor agonism is well known to induce seizures.

DOSAGE AND ADMINISTRATION[72]

It can be administered by oral, intravenous, intramuscular and rectal routes.

It can be administered either as 50mg or 100mg every 4 to 6 hours not exceeding the dosage of 400mg per day.

PHARMACOKINETICS[11,72]

Tramadol has a linear pharmacological profile within the therapeutic range.

Absorption:

Tramadol is almost completely and rapidly administered after oral administration. Maximum plasma concentration (C_{max}) is reached two hours after oral administration. The mean serum concentration after intravenous injection is 1.46 times higher than that of oral administration. Tramadol can be administered without regard to food.

Its bioavailability in oral route is 70-75%, for rectal it is 77% and 100% for intramuscular route

Distribution:

Tramadol is rapidly distributed in the body with a volume of distribution of 2-3 L/kg . It is reduced by 25 percent in those aged above 75 years. Plasma

protein binding is about 20 percent. Tramadol crosses the placental and blood brain barriers.

Metabolism:

Tramadol undergoes hepatic metabolism. It involves demethylation and glucuronidation via cytochrome P450 isozymes and metabolised to five different metabolites. Of these O- desmethyltramadol has 200 times affinity to μ- opioid receptor. Further, it has a elimination half- life of nine hours while that of tramadol is only six hours.

Phase II hepatic metabolism results in water- soluble metabolites which are then excreted by the kidneys. Thus, in renal and hepatic impairment doses may be reduced.

Excretion:

Tramadol and its metabolites are excreted mainly by kidneys (95%). Approximately 15- 19% of an administered dose is excreted as unmetabolised drug which increases in elderly to about 35%.

Tramadol has a half-life of 5-7 hours whreas its metabolite O- desmethyl tramadol has a half-life of 6-8 hours.

DRUG INTERACTIONS[72, 76, 52]

Potentially fatal drug interactions occur with drugs such as serotonergics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonergic antidepressants, certain analgesics (pethidine, oxycodone, dextromethorphan, fentanyl) .certain antibiotics (linezolid, isoniazid), certain anxiolytics,amphetamines, phenethylamine, lithium, methylene blue and a lot other therapeutic agents. Any agents that either induce or inhibit cytochrome P450 are likely to interact with tramadol as it is a substrate of these enzymes.

CLINICAL USES OF TRAMADOL[76, 52, 76, 38, 19]

Tramadol is used in the treatment of moderate to moderately severe pain in both acute and chronic setting.

The European League Against Rheumatism has recommended its use for the management of pain fibromyalgia.

INVESTIGATIONAL USES[40, 41, 76, 36, 11, 82, 84, 101,98, 81]

Diabetic neuropathy

Antidepressant

Postherpetic neuralgia

Acute opioid withdrawal syndrome

Obsessive-compulsive disorder

Premature ejaculation

Post- traumatic stress disorder

ADVERSE EFFECTS[72,81, 48, 10, 13, 75]

Very common: (>10% frequency)

Dizziness

Nausea

Vomiting

Constipation

Headache

Somnolescence

Common:(1-10% frequency)

Anxiety

Dyspepsia

Pruritus

Dry mouth

Malaise

Urinary retention

Visual disturbance

Miosis

Spasticity

Sleep disorder

Uncommon: (0.1-1% incidence)

Palpitation

Tachycardia

Postural hypotension

Gastrointestinal irritation

Urticaria

Flushing

Retching

Rare: (0.01-1% incidence)

Bradycardia

Hypertension

Dyspnoea

Tinnitus

Migraine

Anaphylaxis

Hallucinations

Respiratory depression

Epileptiform convulsions

Stevens – Johnson syndrome

Hepatitis

Liver failure

Pulmonary edema

Gastrointestinal bleeding

Pulmonary embolism

Myocardial ischaemia

REVIEW OF LITERATURE

There are a lot of studies on search for newer drugs apart from opioids for postoperative main management.

Shnekar BF et al.[81] reviewed other studies regarding pregabalin's pharmacology, pharmacokinectics, efficacy and adverse effects in the treatment of neuropathic pain, epilepsy and anxiety. Abstracts from professional meetings were also included. They concluded that pregabalin is effective and safe analgesic, antiepileptic and also an anxiolytic. It will provide a new treatment option for patients with neuropathic pain and partial epilepsy.

Tassone DM et al.[83] reviewed four clinical trials conducted on pregabalin. They finally concluded that pregabalin appears to be effective in treatment of patients with diabetic neuropathy, postherpetic neuralgia and adults with refractory partial-onset seizures. It may also be beneficial in adult patients with general anxiety disorder or social anxiety disorder.

Jokela R et al.[48] conducted a randomized controlled trial of perioperative administration of pregabalin for pain relief after laparascopic hysterectomy. In this study, they evaluated the control of pain after perioperative administration of pregabalin 300 or 600 mg. 91 patients scheduled for laparascopic hysterectomy were randomized to receive either diazepam 10mg, pregabalin 150mg or pregabalin 600 mg as premedication and the dose was repeated after 12 hours except the diazepam group where they received placebo. Until the first postoperative morning, analgesia was provided by oxycodone using patient controlled analgesia. This study concluded that perioperative administration of pregabalin 600mg decreases oxycodone consumption compared with diazepam 10mg but is associated with an increased incidence of side effects.

Burke SMet al.[70] conducted a study in which they evaluated the advantage of perioperative administration of pregabalin in patients undergoing lumbar discectomy. In this study, forty patients were randomly allocated into two groups. They either received placebo or pregabalin. VAS score and the Mc Gill pain Questionaire were noted from preoperatively to 3 months postoperatively. The Roland Morris disability score at the end of 3 months

was less in patients who received pregabalin and the decrease in VAS score was also greater in patients who received pregabalin rather than placebo. Pregabalin administration was associated with greater pain tolerance in both the lower limbs than placebo at 24 hours postoperatively. Pregabalin, a membrane stabiliser, may decrease central senitization and subsequent peripheral pain. Thus perioperative pregabalin administration is associated with less pain intensity and improved functional outcomes 3 months after lumbar discectomy.

Buvanendran A[12] et al. in their study investigated whether a single 300mg dose of pregabalin in patients has sufficient central nervous system bioavailability to be useful under acute conditions where brain or spinal cord excitability may lead to long-term disease, such as chronic pain. Nine patients undergoing total knee replacement received pregabalin 300 mg orally 1 hour before surgery. An intrathecal catheter was inserted for anaesthesia, postoperative analgesic drug administration, and for cerebrospinal fluid sampling. Pregabalin concentration in CSF and plasma was measured using a validated high-pressure liquid chromography assay. It was found that pregabalin concentration in CSF was high 2 hours after administration to have anticonvulsant activity and after 6 hours its high enough to reduce central nervous system hypersensitivity. The median time to peak pregabalin

concentration in CSF was at 8 hours. The study concluded that sufficient central nervous system concentration are reached after oral administration of pregabalin, suggesting that postoperative pain hypersensitivity can be reduced. As this acute pain or spinal cord excitability is decreased, it may prevent chronic pain from developing after surgery.

Jo HR et al.[47] designed a study to confirm whether remifentanil given during propofol anaesthesia induced postoperative pain sensitization and pregabalin given could prevent this pronociceptive effect. Patients were randomly allocated into three groups. The control group received placebo and intraoperative saline infusion, second group received placebo as premedication and an intraoperatuve infusion of remifentanil, the third group received pregabalin 150 mg as premedication and remifentanil infusion.VAS scores as well as postoperative opiod requirement were noted. The results of this study shows that remifentanil added to propofol anaesthesia causes pain sensitization in the immediate postoperative period. Pretreatment with pregabalin prevents this pronociceptive effect and so this may be useful for the management of acute postoperative pain when remifentanil and propofol are used as anaesthetics.

Choi YS et al.[20] conducted a study using a combination of pregabalin and dexamethasone for evaluating the postoperative pain and functional outcome in patients undergoing lumbar spinal surgery. In this randomised-controlled study,one hundred and eight patients were randomised into three groups. Group C received placebo+placebo, group P received pregabalin+placebo and group PD received pregbalin+dexamethasone. The pain intensity and side effects were assessed in the postoperative period upto 72 hours. Pain intensity and daily activity performance were also assessed 1, 3 and 6 months after surgery. Compared to group C, the pain scores were lower in group PD 24 hours after surgery and the frequency of additional rescue doses were significantly lower in group PD until 48 hours after surgery. The same were lower in group P for 24 to 48 hours relative to group C. Daily activity performance was better in group PD compared with group C at 1 month after surgery. This study concludes that combined administration of pregabalin and dexamethasone conferred analgesic benefits superior to those of pregabalin alone. Further it also facilitated the return to normal activity after surgery.

Joshi SS et al.[50] conducted a study evaluating the efficacy of perioperative pregabalin on acute and chronic postoperative pain after off-pump coronary artery bypass (OPCAB) surgery. Patients were randomised to pregabalin and control groups. Pregabalin group received 150mg pregabalin 2 hours prior to

induction of anaesthesia and 75 mg twice daily for two postoperative days whereas the control group received placebo at similar timings. VAS score and sedation score were observed upto 48 hours after extubation. Time to extubation, tramadol consumption and side effects were also noted. The study concluded that perioperative pregabalin reduced pain scores at rest and deep breath and also reduced the consumption of tramadol in the post operative period without causing any delay in extubation or excess sedation.

Garcia RM et al.[31] conducted a study to assess the efficacy of a novel multimodal analgesic regimen in reducing postoperative pain and intravenous morphine requirements after primary multilevel lumbar laminectomy. 22 patients were randomly assigned to receive either only intravenous morphine or a multimodal analgesic regimen (celecoxib, pregabalin, extended release oxycodone). Postoperatively all patients received intravenous morphine as and when needeed.VAS scores upto 36 hours and total morphine requirement were noted. Patients demonstrated lower intravenous morphine requirements, better pain score and earlier time to solid food intake. The study concluded that opioid and nonopioid combinations appear to be safe and effective after lumbar laminectomy.

In their study, Balaban F et al.[22] analysed the efficacy of two different doses of preoperative pregabalin (150 mg and 300 mg) on pain relief and total opioid consumption after laparascopic cholecystectomy. Postoperative VAS scores, Ramsay sedation score and Aldrette scores were measured upto 24 hours after surgery. Additional opioid requirement and side effects if any, were also noted. The results of this study showed that preemptive pregabalin decreased pain scores and postoperative fentanyl requirement in patients undergoing laparascopic cholecystectomy in a dose dependent manner. There was also no difference in side effects between the two different groups on two different dosages.

George RB et al.[33] performed a study to determine if low dose of pregabalin could decrease opioid use following abdominal hysterectomy while comparing placebo. Patients were randomised into three groups- pregabalin 75 mg (P75), pregabalin 150 mg (P150) or placebo. The study drug was administered two hours prior to surgery and 12 hour following the initial dose. Postoperative pain was managed using patient controlled analgesia with morphine. Pain at rest and movement as well as complications like nausea,vomiting were also assessed. Mean cumulative morphine consumption postoperatively was noted. This clinical trial showed pregabalin treatment may not be use in reducing opioid use upto 24 hours postoperatively.

Meet JM et al.[61] conducted a study in which patients undergoing photorefractive keratectomy were given pregabalin 75mg twice daily for five days whereas the control group received placebo. Both groups received the standard pain care regimen. It was found that in pregabalin group there was lower pain scores and the frequency of rescue pain medications were also low.

Aydogan H et al.[4] conducted a study by administering a single oral dose of 75mg of pregabalin to patients undergoing percutaneous nephrolithotomy. They evaluated the effect of pregabalin on postoperative pain scores, analgesic consumption and side effects. They found that pregabalin is effective in reducing early postoperative pain scores and total analgesic consumption without any hemodynamic instability or side effects.

MATERIALS AND METHODS

After obtaining institutional ethical commmitee approval and informed consent, the study was conducted in 75 patients belonging to American Society of Anaesthesiology- 1 (ASA) and ASA- 2 of either sex and age group between 20-60 years undergoing elective decompressive lumbar laminectomy.

This a prospective, randomised, single blinded study.

The study was conducted in Rajiv Gandhi Government General Hospital, Madras Medical College.

The patients were randomised into three groups of 25 patients each by closed envelope method. The patients were blinded to the group they belong.

INCLUSION CRITERIA

Age – 20 years to 60 years

Weight - 40 to 70 kilograms

BMI - < 30 kilograms/metre square

ASA- 1 & 2

Surgery- elective lumbar decompressive laminectomy

Patients who have given valid informed written consent.

EXCLUSION CRITERIA

Patients not satisfying inclusion criteria

Patients posted for emergency surgery

Patients with renal insufficiency

Patients with liver disease

History of allergy or sensitivity to the drugs used

History of seizure disorder

Chronic therapy with opioids.

PRIMARY AND SECONDARY OUTCOME

The primary outcome of the study was to measure the analgesic and anxiolytic efficacy of pregabalin and tramadol for postoperative pain while the secondary outcome was to assess the intraoperative hemodynamics and adverse effects of these drugs.

MATERIALS

Pregabalin capsules 150mg

Tramadol capsules 100mg

Placebo capsules

Drugs- Injection Midazolam, Injection Glycopyrrolate, Inj Fentanyl, Inj.Thiopentone Sodium, Inj. Vecuronium, Inj. Neostigmine, Sevoflurane, emergency drugs, Normal Saline and Ringer Lactate.

Monitors- ECG, NIBP, SPO2, EtCo2.

STUDY DESIGN

The patients satisfying inclusion criteria were randomly allocated into three groups each containing 25 patients. Randomisation was done by closed envelope method.

Group 1(placebo)- received a placebo capsule orally 1 hour before anaesthetic induction.

Group 2 (tramadol)- received a tramadol capsule 100mg orally 1 hour before anaesthetic induction.

Group 3(pregabalin)- received a pregabalin capsule 150mg 1 hour before anaesthetic induction.

All patients were visited the evening before surgery. They were explained about the study methods, the visual analogue scale chart and were provided with information sheet. All were orally premedicated with alprazolam 0.5mg at 10.00 pm, the previous night of surgery.

ANAESTHESIA PROTOCOL

The patients were premedicated with an injection of midazolam (0.05mg/kg) i.v. and an injection of glycopyrrolate (0.005mg/kg) i.v. Analgesia was provided with Injection fentanyl 2mic/kg and induction was done with

thiopentone sodium (5 mg/kg of 2.5% solution).Endotracheal intubation was facilitated by using vecuronium bromide as muscle relaxant in the dosage of 0.1mg/kg. Anaesthesia was maintained with N_2O:O_2 (66:33) and with sevoflurane.

Standard monitoring included non invasive blood pressure monitoring, electrocardiogram, end tidal concentration of carbon dioxide and pulse oximetry.

Intravenous fluids, Normal Saline and Ringer's Lactate, were administered at the rate of 100 ml/hour. There was minimal blood loss in the surgery.

All patients were given antiemetic ondansetron 4mg i.v.

At the end of the surgery, patients were extubated after the reversal of the residual neuromuscular blockade with inj.neostigmine (0.05 mg/kg) and inj. glycopyrrolate (0.01 mg/kg).

Postoperatively, whenever patients complained of pain (Visual Analog Score of more than 3) they received 0.5mic/kg of fentanyl as rescue analgesia, which was repeated until the pain subsided.

Pain quantification was done on a modified Visual Analog Scale Score between 0 and 10 (0 = no pain to 10 = worst imaginable pain.[88]

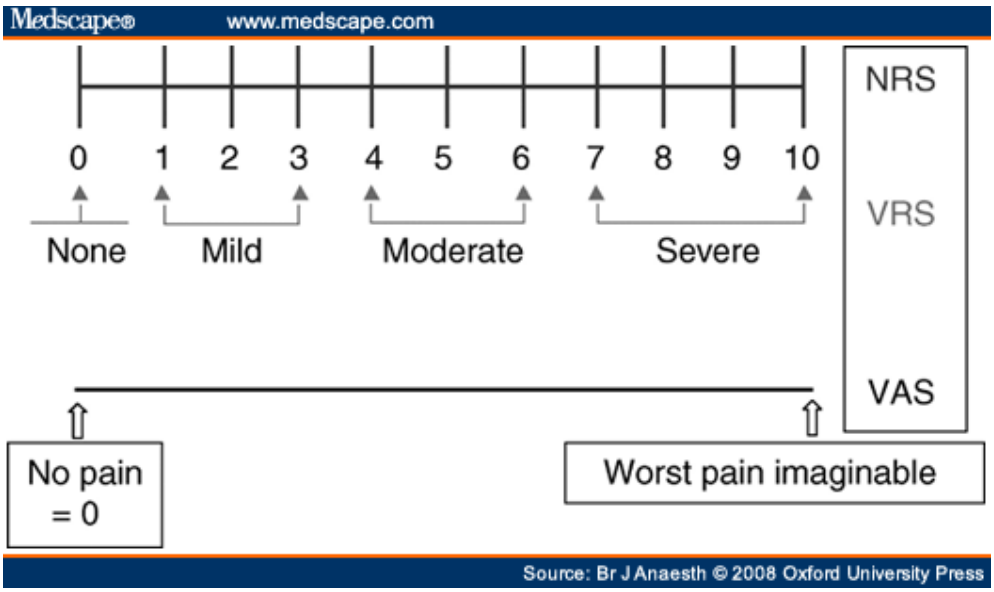

Figure 10.1 Visual Analog Scale Scoring

Sedation scores were based on Ramsay Sedation Scale.

RAMSAY SEDATION SCALE[74]

1— Patient anxious, agitated or restless or both

2— Patient co-operative, oriented and tranquil

3— Patient responds to commands only

4— Patient sedated with brisk response to stimulus

5— Patient sedated with sluggish response to stimulus

6— Patient sedated with no response to stimulus

[Stimulus indicates a light glabellar tap or loud command at ears]

ANXIETY SCORES[75] were given by

1— fearful/afraid

2— worried

3— anxious

4— uneasy

5— calm and comfortable

The pain scores, sedation scores, anxiety scores were recorded preoperatively, after extubation then at 1, 2, 4 and 6 hours.

Baseline heart rate, systolic bloood pressure, diastolic blood pressure, mean arterial pressure, respiratory rate, saturation were recorded. Heart rate, systolic and diastolic blood pressure, mean arterial pressure were recorded preoperatively and during various time intervals intraoperatively and after extubation.

Postoperative blood pressure, heart rate, respiratory rate, postoperative pain, sedation, anxiety, total analgesic consumption were recorded at the end of 6 hours.

Side effects like nausea, vomiting, drowsiness, constipation and other complications, if any, were also recorded preoperatively, as well as 1, 2, 4 and 6 hours after extubation.

STATISTICAL ANALYSIS

Sample size was estimated by conducting a pilot study in 5 patients. The sample size needed was 50 for the power of the study to be 50% and alpha erroe to be 0.05. hence, considering the drop outs the sample size was chosen as 75.

The statistical analysis was done using SPSS software version 20. Qualitative analysis between the three groups was done by ANOVA and quantitative analysis by chi- square test.

OBSERVATION AND RESULTS

The study was done in 75 patients of either sexes in the age group of 20 to 60 years, belonging to ASA class-1 and ASA class- 2, undergoing elective lumbar laminectomy under general anaesthesia.

The patients were categorised into three groups

Group 1 - placebo

Group 2 - tramadol

Group 3 - pregabalin

DEMOGRAPHIC PROFILES

The demographic profiles like age, sex, weight, height, BMI, ASA status were comparable between the three groups as shown in table 11.1.

Table 11.1 : Demographic profiles of the three groups

Demographic profile	**Group1 (Mean±SD)**	**Group 2 (Mean±SD)**	**Group3 (Mean± SD)**	**P value**
Age (years)	44.04 ± 7.44	44.12 ± 8.52	45.96 ± 8.5	0.645
Sex (M:F)	8:17	9:16	8:17	0.942
Weight (Kg)	56.44 ± 7.19	57.64 ± 7.49	56.88 ± 6.18	0.828
Height (metre)	1.56 ± 0.07	1.57 ± 0.07	1.59 ± 0.09	0.404
BMI (kg/m^2)	23.35 ± 1.74	23.20 ± 2.04	22.53 ± 1.14	0.192
ASA class 1:2	13:12	13:12	12:13	0.948

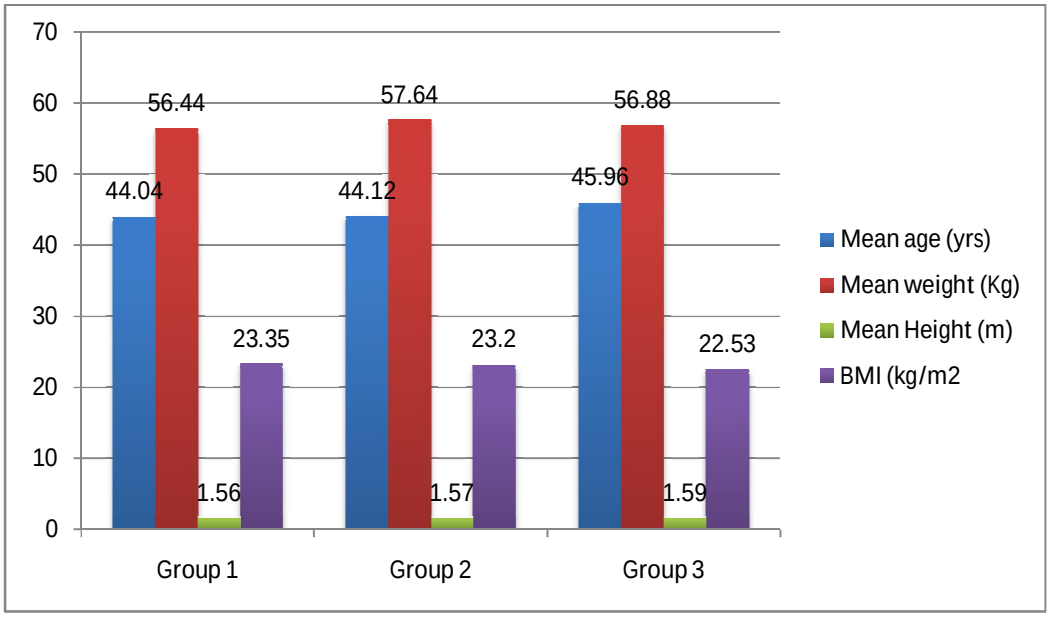

Figure 11.1: Comparison of demographic data among all the groups

The mean age of patients in group1 is 44.04 with a standard deviation of 7.44 and in group 2 the mean age is 44.12 with a standard deviation of 8.52 and in group 3 the mean age is 45.96 with a standard deviation of 8.5. The p value is 0.645, which is insignificant. So all the three groups are comparable in terms of age.

The mean weight of the patients in group 1 is 56.44 with a standard deviation of 7.19 and in group 2 are 57.44 with a standard deviation of 7.49 and in group 3 are 56.88 with a standard deviation of 6.18. The p value is found to be 0.828 which is not significant. Therefore the three groups are comparable in their weight.

The mean height of patients in group1, group 2 and group 3 are 1.56, 1.57and 1.59 with a standard deviation of 0.07, 0.07 and 0.09 respectively. The p value is found to be 0.404 which is not significant. This implies that there is no significant difference in height among the three groups and they are comparable.

The mean body mass index among group 1, group 2 and group 3 are 23.35, 23.20 and 22.53 with a standard deviation of 1.74, 2.04 and 1.14 respectively. The p value is 0.192 which is not significant. Therefore the body mass index is comparable among all the three groups.

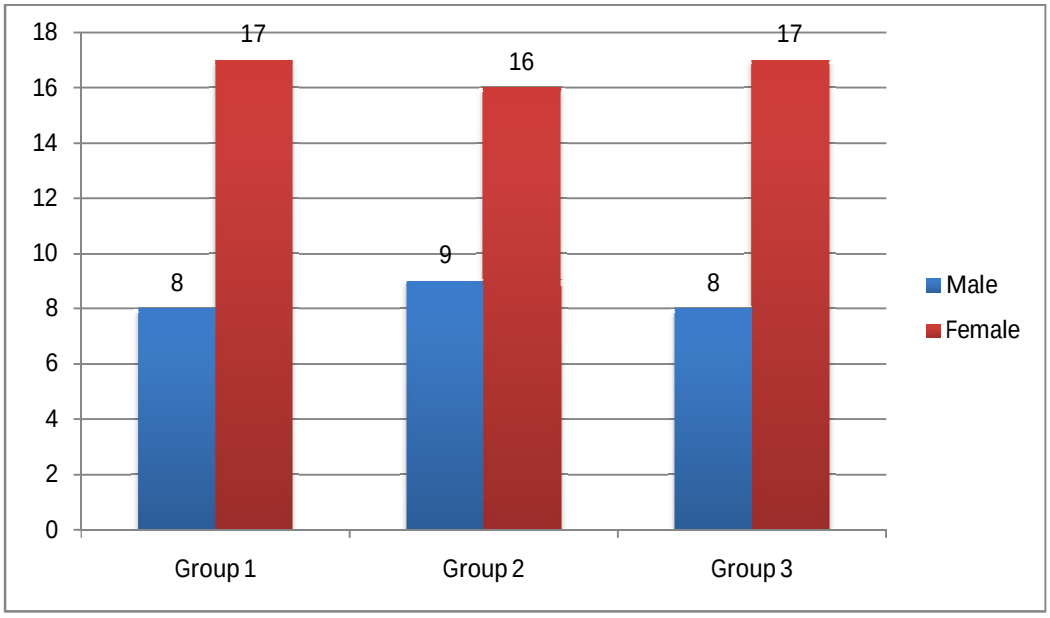

Figure 11.2 Comparison of demographic data (gender distribution)

The figure 11.2 shows the gender distribution among all the three groups. The sex ratio (male:female) among group 1, group 2 and group 3 are 8:17, 9:16 and 8:17 respectively. The p value is found to be 0.942 which is not significant which shows the gender distribution among all the three groups is comparable.

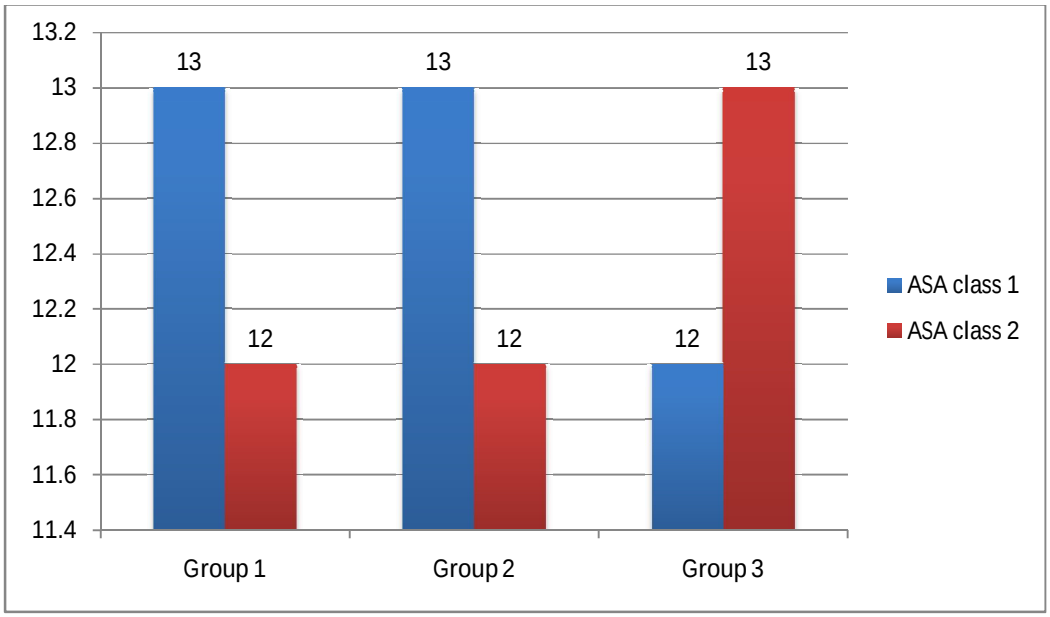

Figure 11.3 Comparison of ASA status among all the groups

The figure 11.3 shows the ASA status among all three groups. The ASA class1:2 ratios among the three groups 1, 2 & 3 are 13:12, 13:12 & 12:13 respectively. The p value is found to be 0.948 which is not significant. This implies that the ASA status among all the three groups is comparable.

Table 11.2 Duration of surgery and Spinal levels

	Group-1 Mean±SD)	**Group-2 (Mean±SD)**	**Group-3 (Mean±SD)**	**P value**
Duration of surgery (minutes)	148.00±15.00	144.80±11.3	146.40±17.29	0.63
Spinal levels (1:2)	12:13	11:14	13:12	0.852

The mean duration of surgery in minutes among group 1, group 2 and group 3 are 148±15, 148.80±11.3 and 146.40±17.29 respectively. The p value is found to be 0.63 which is insignificant. This shows that the mean duration of surgery among the three groups is comparable.

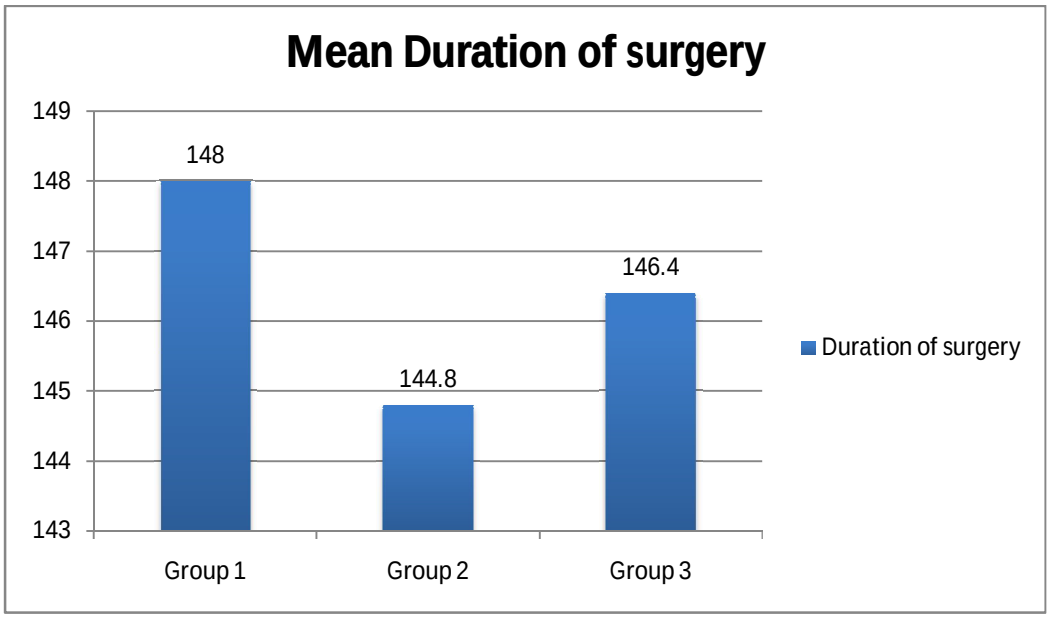

Figure 11.4 Mean duration of surgery among the three groups

The spinal levels of laminectomy (1:2) in group 1, group 2 and group 3 are 12:13, 11:14 and 13:12 respectively with a p value of 0.852 which shows that the groups are comparable.

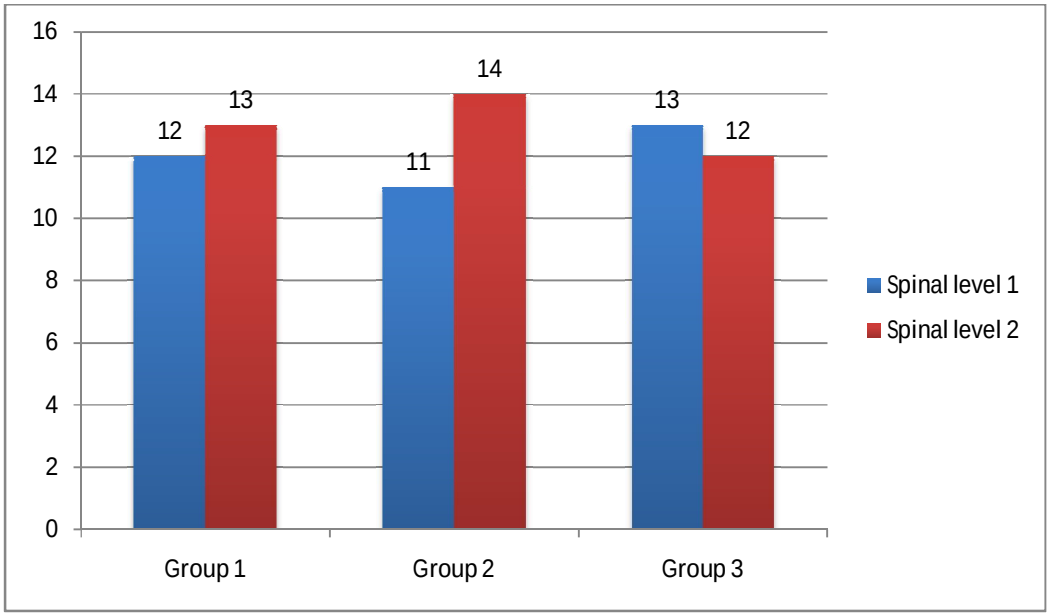

Figure 11.5 Number of spinal segments operated among all the three groups

Table 11.3 Baseline hemodynamic parameters of the three groups

Parameter	Group-1 (Mean±SD)	Group-2 (Mean±SD)	Group-3 (Mean±SD)	P-value
Heart rate	75.12 ± 4.49	74.84 ± 7.11	74.28 ± 6.60	0.422
Systolic blood pressure	122.00 ±11.09	122.24 ± 9.18	122.64 ±8.41	0.381
Diastolic blood pressure	78.92± 6.32	78.92 ± 9.10	78.04± 5.19	0.117
Mean arterial blood pressure	93.16± 7.64	93.24 ± 8.151	93.16 ± 5.41	0.101

The mean baseline heart rate of group 1, group 2 and group 3 are 75.12±4.49, 74.84±7.11 and 74.28±6.60 respectively with a p value of 0.422 which is insignificant. The mean baseline systolic blood pressures of group 1, group 2 and group 3 are 122±11.09, 122.24±9.18 and 122.64±8.41 respectively with a p value of 0.381 which is not significant. The mean baseline diastolic blood pressure of group1, group 2 and group 3 are 78.92±6.32, 78.92±9.10 and 78.04±5.19 respectively with a p value of 0.117 which is insignificant. The mean baseline MAP of group 1, 2 &3 are 93.16±7.64, 93.24±8.151and 93.16±5.41 respectively with a p value of 0.101 which is insignificant.

Thus all three groups are comparable in their baseline hemodynamic parameters.

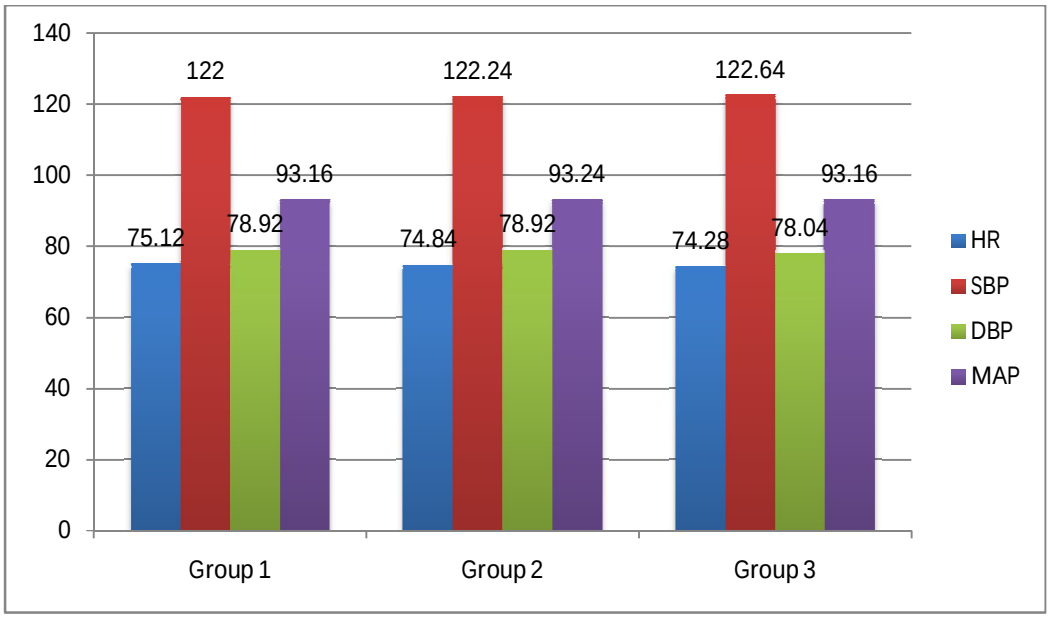

Figure 11.6 Comparison of Baseline hemodynamic parameters among all the groups

Table 11.4 Comparison of Baseline hemodynamic parameters among group 1 & 2

Parameter	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Mean difference(1-2)	p-value
Heart rate	75.12 ± 4.49	74.84 ± 7.11	2.28	0.587
Systolic blood pressure	122.00±11.09	122.24±9.18	3.760	0.514
Diastolic blood pressure	78.92± 6.32	78.92 ± 9.10	3.120	0.368
Mean Arterial blood pressure	93.16 ± 7.64	93.24±8.151	3.720	0.212

The p values of baseline heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressures between group 1 and 2 are insignificant and therefore the two groups are comparable

Table 11.5 Comparison of Baseline hemodynamic parameters between group 1 & 3

Parameter	Group-1 (Mean±SD)	Group-3 (Mean±SD)	Mean difference(1-3)	p-value
Heart rate	75.12 ± 4.49	74.28 ± 6.60	0.840	1.000
Systolic blood pressure	122.00±11.09	122.64 ±8.41	0.640	1.000
Diastolic blood pressure	78.92± 6.32	78.04± 5.19	0.880	1.000
Mean Arterial blood pressure	93.16 ± 7.64	93.16 ± 5.41	0.000	1.000

The above table shows the comparison of baseline hemodynamic variables between group 1 and 3. From the p values we know that group 1 and 3 are comparable.

Table 11.6 Trend in the heart rate

Heart rate	Group 1 (Mean±SD)	Group 2 (Mean ± SD)	Group 3 (Mean±SD)	P value
Pre-op	80.36± 5.65	78.08 ± 6.44	80.32± 7.22	0.366
AI -1 min	90.52 ± 9.59	82.20± 5.06	82.48± 5.44	0.000#
AI -3 min	87.64 ± 8.61	81.88± 8.38	82.88± 7.80	0.026#
AI -5 min	81.44 ± 8.65	76.20 ± 7.19	77.76 ± 7.36	0.056
30 min	81.48 ± 4.71	72.56 ± 5.95	75.32 ± 6.38	0.000#
60 min	82.68 ± 5.23	71.36 ± 6.49	76.12 ± 7.02	0.000#
120 min	81.48 ± 4.71	70.92 ± 6.78	77.32 ± 6.46	0.000#
AE	97.76 ± 8.56	86.20 ± 6.81	91.68 ± 7.76	0.000#

#- p value significant

The mean heart rate changes during different time intervals in group 1, 2 & 3 are shown in the above table. The p value appears to be significant in all the time intervals except preoperatively and five minutes after intubation.

The groups are individually compared in the following tables.

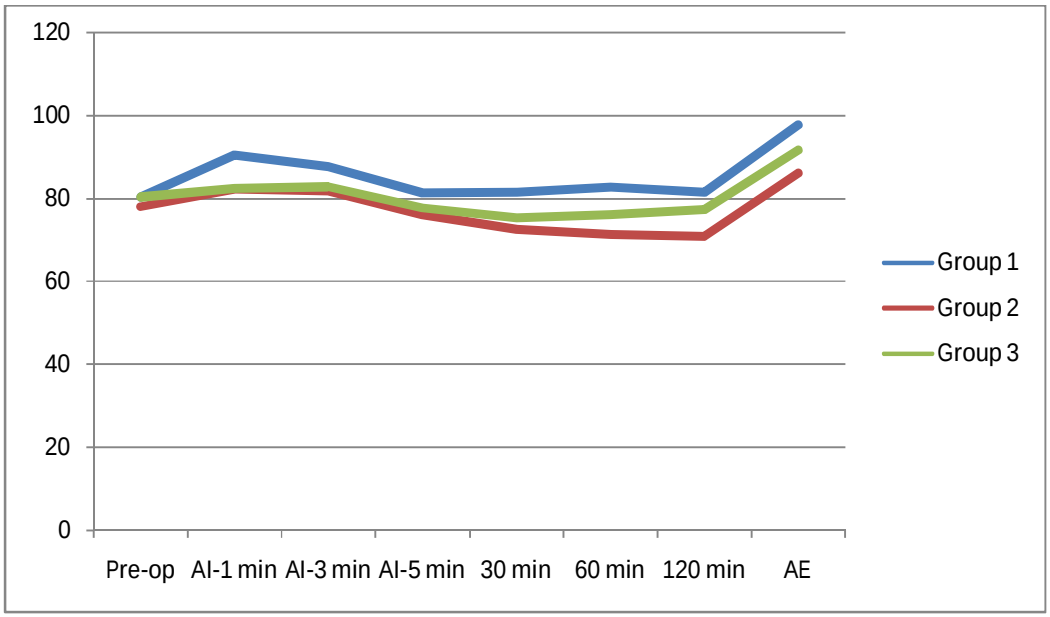

Figure 11.7 Trend in the heart rate during various time intervals

Table 11.7 Heart rate changes between group 1& 2 during various time intervals

HeartRate	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Mean difference (1-2)	P value
Pre-op	80.36± 5.65	78.08 ± 6.44	2.280	0.674
AI -1 min	90.52 ± 9.59	82.20± 5.06	8.32	0.000#
AI -3 min	87.64 ± 8.61	81.88± 8.38	5.760	0.050#
AI -5 min	81.44 ± 8.65	76.20 ± 7.19	5.240	0.059
30 min	81.48 ± 4.71	72.56 ± 5.95	8.920	0.000#
60 min	82.68 ± 5.23	71.36 ± 6.49	11.320	0.000#
120 min	81.48 ± 4.71	70.92 ± 6.78	10.560	0.000#
AE	97.76 ± 8.56	86.20 ± 6.81	11.560	0.000#

#- p value significant

The comparison of heart rate changes between group 1 & 2 showed significant difference at 1 minute & 3 minutes after intubation and at 30, 60 and 120 min and after extubation.

Table 11.8 Comparison of heart rate changes between group 1 & 3 at various time intervals

Heart Rate	Group 1 (Mean±SD)	Group 3 (Mean±SD)	Mean difference (1-3)	P value
Pre-op	80.36± 5.65	80.32± 7.22	0.040	1.000
AI -1 min	90.52 ± 9.59	82.48± 5.44	8.040	0.010#
AI -3 min	87.64 ± 8.61	82.88± 7.80	4.760	0.049#
AI -5 min	81.44 ± 8.65	77.76 ± 7.36	3.680	0.294
30 min	81.48 ± 4.71	75.32 ± 6.38	6.160	0.001#
60 min	82.68 ± 5.23	76.12 ± 7.02	6.560	0.001#
120 min	81.48 ± 4.71	77.32 ± 6.46	4.160	0.040#
AE	97.76 ± 8.56	91.68 ± 7.76	6.080	0.001#

- p value significant

The comparison of heart rate changes between group 1 & 3 showed significant difference at 1 and 3 minutes after intubation, at 30, 60 and 120 minutes and after extubation.

Table 11.9 Trend in the systolic blood pressure

SBP	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Group 3 (Mean±SD)	P value
Pre-op	124.00 ± 11.09	119.04 ± 8.35	119.12±9.93	0.133
AI-1 min	152.16 ± 22.09	125.04 ± 9.99	134.76 ± 15.64	0.000#
AI-3 min	129.16 ± 14.59	115.92 ± 16.49	119.56±7.92	0.003#
AI-5 min	122.28 ± 13.87	116.12 ± 9.19	116.64± 11.42	0.068
30 min	118.96 ± 12.37	108.76 ± 8.07	112.28 ± 10.55	0.018#
60 min	123.16 ± 12.16	111.00± 9.22	113.36 ± 10.41	0.007#
120 min	119.96 ± 12.37	114.48± 8.74	115.48 ± 10.48	0.265
AE	148.44 ± 20.61	117.28 ± 11.04	131.80 ± 15.71	0.000#

#- p value significant

From the above table it appears that the systolic blood pressure changes among the three groups at 1& 3 minute after intubation and at 30 min, 60 minutes and after extubation is significant ($p<0.05$).

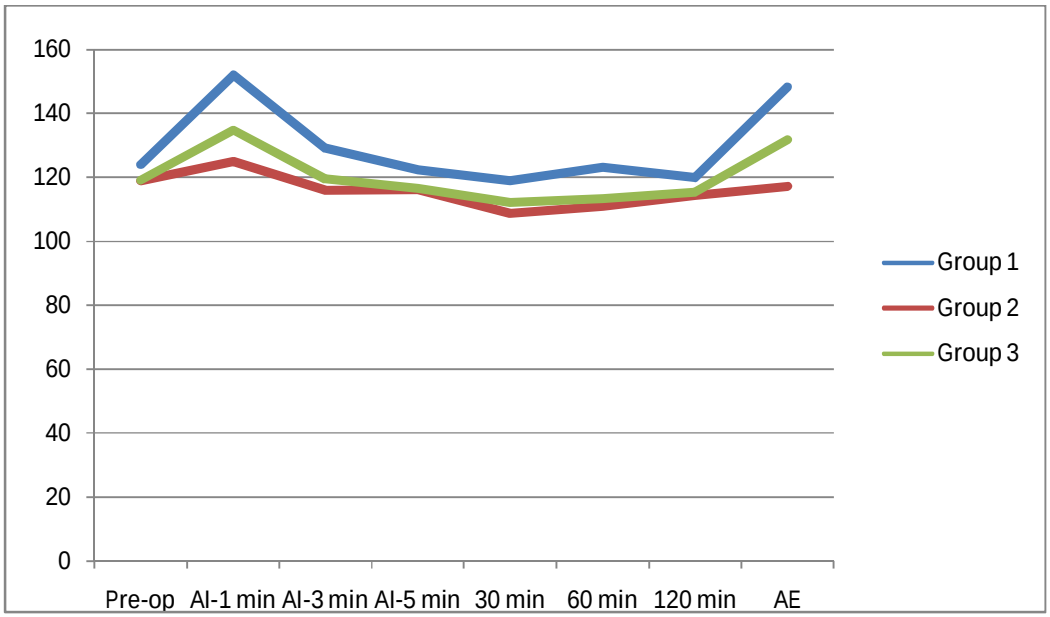

Figure 11.8 Trend in the systolic blood pressure among the three groups

Table 11.10 Systolic blood pressure changes between group 1 & 2

SBP	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Mean difference (1-2)	P value
Pre-op	124.00 ±11.09	119.04 ± 8.35	4.960	0.238
AI-1 min	152.16 ±22.09	125.04 ± 9.99	27.120	0.000#
AI-3 min	129.16 ±14.59	115.92 ± 16.49	13.240	0.043#
AI-5 min	122.28 ±13.87	116.12 ± 9.19	6.16	0.150
30 min	118.96 ±12.37	108.76 ± 8.07	10.20	0.085
60 min	123.16 ±12.16	111.00± 9.22	12.16	0.079
120 min	119.96 ±12.37	114.48± 8.74	5.48	0.212
AE	148.44 ±20.61	117.28 ± 11.04	31.160	0.000#

 # - p value significant

The systolic blood pressure changes are significant between the groups 1 & 2 at 1 and 3 minutes after intubation and after extubation ($p < 0.05$).

Table 11.11 Systolic blood pressure changes between group 1 & 3

SBP	Group 1 (Mean±SD)	Group 3 (Mean±SD)	Mean difference (1-3)	P value
Pre-op	124.00 ± 11.09	119.12±9.93	4.880	0.253
AI-1 min	152.16 ± 22.09	134.76 ± 15.64	17.400	0.001#
AI-3 min	129.16 ± 14.59	119.56±7.92	9.600	0.099
AI-5 min	122.28 ± 13.87	116.64± 11.42	5.640	0.274
30 min	118.96 ± 12.37	112.28 ± 10.55	6.680	0.100
60 min	123.16 ± 12.16	113.36 ± 10.41	9.80	0.094
120 min	119.96 ± 12.37	115.48 ± 10.48	4.48	0.278
AE	148.44 ± 20.61	131.80 ± 15.71	16.640	0.002#

- p value significant

From the above table it is clear that the systolic blood pressure is significantly ($p<0.05$) decreased in group 3 when compared to group 1 at 1 minute after intubation and after extubation. In all other time intervals the mean systolic blood pressure in group 3 is less than that of group 1 but is insignificant ($p>0.05$).

Table 11.12 Trend in the diastolic blood pressure

DBP	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	P value
Pre -op	78.28 ± 7.36	76.56 ± 9.38	77.44 ± 5.75	0.855
AI-1 min	99.52 ± 14.44	84.20 ± 11.84	90.96± 10.51	0.000#
AI-3 min	83.92 ± 9.88	75.56 ± 11.96	80.20 ± 11.26	0.033#
AI-5 min	81.28 ± 9.82	76.80 ± 7.33	79.72 ± 8.55	0.183
30 min	73.52 ± 8.45	70.40 ± 5.78	72.80 ± 5.78	0.270
60 min	75.20 ± 8.40	71.44 ± 5.65	74.60 ± 9.26	0.130
120 min	73.52 ± 8.45	70.40 ± 9.42	72.40 ± 5.78	0.384
AE	93.96 ± 21.65	79.88 ± 9.06	88.04 ± 11.02	0.006#

#- p value significant

The diastolic blood pressure of group 1, 2 & 3 is statistically significant at 1, 3 minute after intubation and after extubation ($p<0.05$).

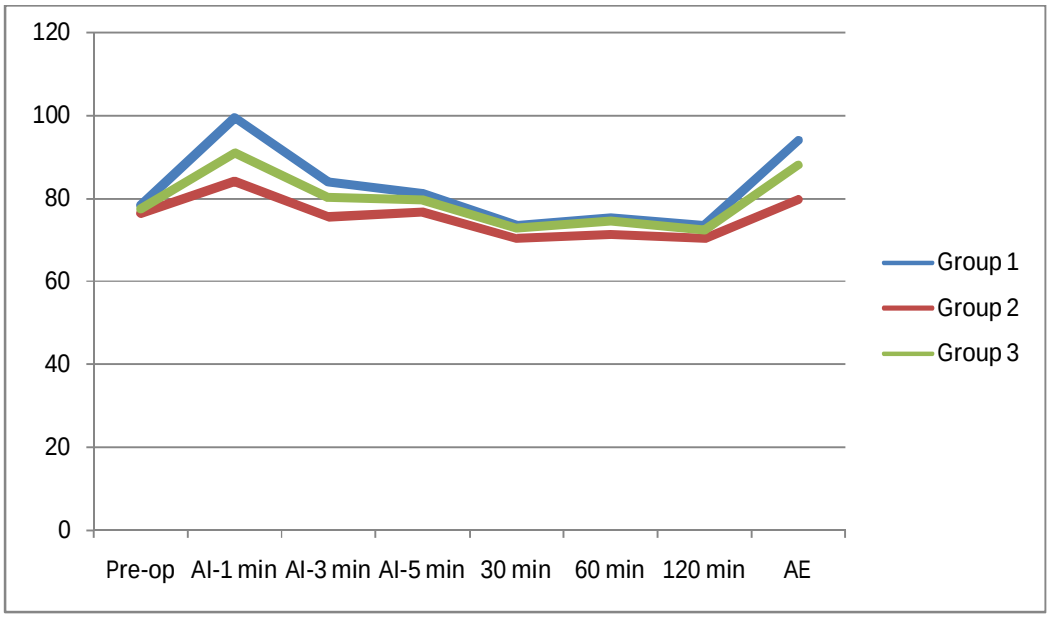

Figure 11.9 Trend in the diastolic blood pressure

Table 11.13 Diastolic blood pressure changes between group 1 & 2

DBP	Group 1 (Mean±SD)	Group 2 (Mean ± SD)	Mean difference (1-2)	P value
Pre -op	78.28 ± 7.36	76.56 ± 9.38	01.72	1.000
1 min	99.52 ± 14.44	84.20 ± 11.84	15.32	0.000#
3 min	83.92 ± 9.88	75.56 ± 11.96	08.36	0.028#
5 min	81.28 ± 9.82	76.80 ± 7.33	04.48	0.211
30 min	73.52 ± 8.45	70.40 ± 5.78	03.12	0.518
60 min	75.20 ± 8.40	71.44 ± 5.65	03.76	0.293
120 min	73.52 ± 8.45	70.40 ± 9.42	03.12	0.521
AE	93.96 ± 21.65	79.88 ± 9.06	14.08	0.004#

- p value significant

The mean diastolic blood pressure of group 2 is significantly decreased than that of group 1 at 1 & 3 minute after intubation and after extubation ($p<0.05$).

In all other time intervals there is no significant decrease between the two groups.

Table 11.14 Diastolic blood pressure changes in group 1and 3

DBP	Group 1 (Mean±SD)	Group 3 (Mean ± SD)	Mean difference (1-3)	P value
Pre -op	78.28 ± 7.36	77.44 ± 5.75	00.84	1.000
1 min	99.52 ± 14.44	90.96± 10.51	08.56	0.049#
3 min	83.92 ± 9.88	80.20 ± 11.26	03.72	0.716
5 min	81.28 ± 9.82	79.72 ± 8.55	01.56	1.000
30 min	73.52 ± 8.45	72.80 ± 5.78	00.72	1.000
60 min	75.20 ± 8.40	74.60 ± 9.26	00.60	1.000
120 min	73.52 ± 8.45	72.40 ± 5.78	01.12	1.000
AE	93.96 ± 21.65	8.04 ± 11.02	09.92	0.040#

- p value significant

The mean diastolic blood pressure of group 3 is significantly less ($p<0.05$) in group 3 when compared to group 1 at 1 minute after intubation and after extubation. The difference in mean diastolic blood pressure is insignificant between group 1 & 3 in rest of the time intervals.

Table 11.15 Trend in the mean arterial blood pressure

MAP	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	P value
Pre-op	93.28 ± 7.70	90.12 ± 8.57	91.60 ± 9.77	0.365
1 min	117.48 ± 18.07	97.08 ± 9.15	104.40 ± 13.38	0.000#
3 min	98.36 ± 11.05	87.64 ± 9.25	88.44 ± 13.30	0.011#
5 min	94.24 ± 10.40	87.88 ± 7.87	88.44 ± 9.15	0.050
30 min	86.88± 9.68	82.64± 7.88	83.88± 6.38	0.117
60 min	88.16 ± 9.17	80.66± 8.22	84.72± 6.63	0.038
120 min	86.60± 9.39	82.40 ± 8.34	84.80± 6.58	0.519
AE	114.16 ± 16.20	91.68± 8.93	102.44± 12.14	0.000#

- p value significant

The mean arterial blood pressure between group 1, 2 and 3 shows significant difference at 1 and 3 minutes after intubation and after extubation.

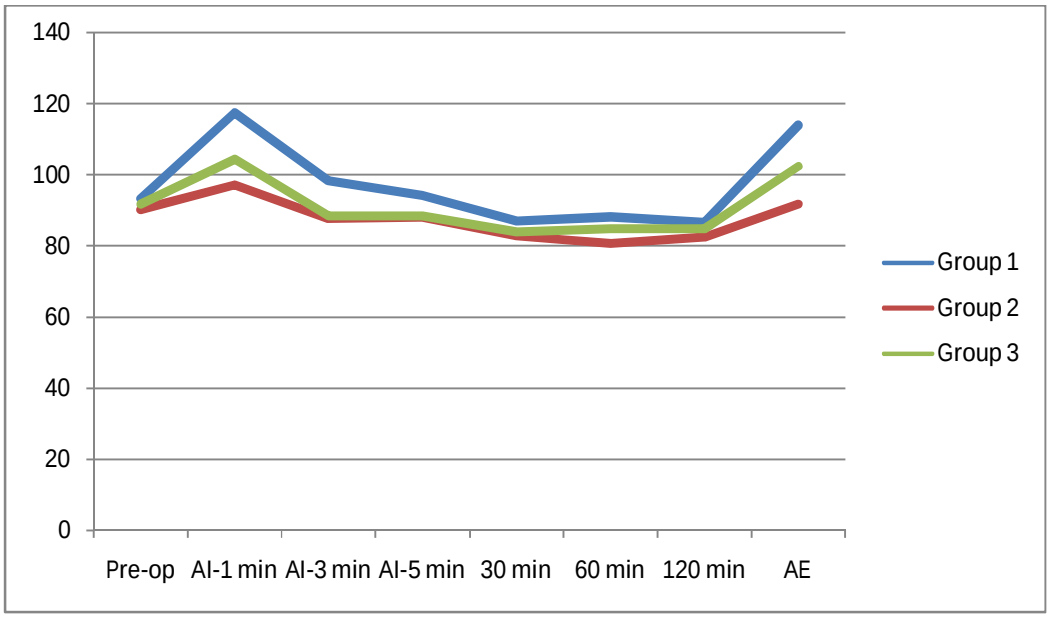

Figure 11.10 Trend in the mean arterial blood pressure

Table 11.16 Mean arterial blood pressure changes in group 1 & 2

MAP	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Mean difference (1-2)	P value
Pre-op	93.28 ± 7.70	90.12 ± 8.57	03.160	1.000
1 min	117.48 ± 18.07	97.08 ± 9.15	20.400	0.000#
3 min	98.36 ± 11.05	87.64 ± 9.25	10.720	0.044#
5 min	94.24 ± 10.40	87.88 ± 7.87	06.360	1.000
30 min	86.88 ± 9.68	82.64 ± 7.88	04.240	1.000
60 min	88.16 ± 9.17	80.66 ± 8.22	07.500	0.821
120 min	86.60 ± 9.39	82.40 ± 8.34	04.200	1.000
AE	114.16 ± 16.20	91.68 ± 8.93	22.480	0.000#

 # - p value significant

The mean arterial pressure in group 2 is less than that of group 1 in all the time intervals but is significantly less at 1 and 3 minutes after intubation and after extubation

Table 11.17 Mean arterial blood pressure changes in group 1 and 3

MAP	Group 1 (Mean±SD)	Group 3 (Mean±SD)	Mean difference (1-3)	P value
Pre-op	93.28 ± 7.70	91.60 ±9.77	01.680	0.663
1 min	117.48 ± 18.07	104.40 ± 13.38	13.080	0.005#
3 min	98.36 ± 11.05	88.44 ± 13.30	09.920	0.051
5 min	94.24 ± 10.40	88.44 ± 9.15	05.800	0.087
30 min	86.88 ± 9.68	83.88 ± 6.38	03.000	0.582
60 min	88.16 ± 9.17	84.72 ± 6.63	03.440	0.409
120 min	86.60 ± 9.39	84.80 ± 6.58	01.800	1.000
AE	114.16 ± 16.20	102.44 ± 12.14	11.720	0.005#

 # - p value significant

The mean arterial pressure in group 3 is significantly decreased at 1 minute after intubation and after extubation while there is no significant difference in mean arterial blood pressure between the groups in rest other time intervals.

Table 11.18 Pain scores in the three groups

VAS	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	P value
Pre-op	1.52 ± 0.510	0.68± 0.476	1.48± 0.510	0.000#
AE	4.84± .624	1.48± .510	3.12 ± 0.332	0.000#
1 hr	5.52± 0.510	2.00± 0.408	2.84± 0.374	0.000#
2 hr	6.48± 0.510	2.40± 0.500	3.40± 0.500	0.000#
4 hr	5.80± 0.408	2.32± 0.476	4.12± 0.332	0.000#
6 hr	5.72 ± 0.458	2.52 ± 0.510	4.08± 0.277	0.000#

 # - p value significant

The mean Visual Analog Scale scoring in group 2 is less than group 3, which is less than group 1. This difference is significant ($p<0.05$)

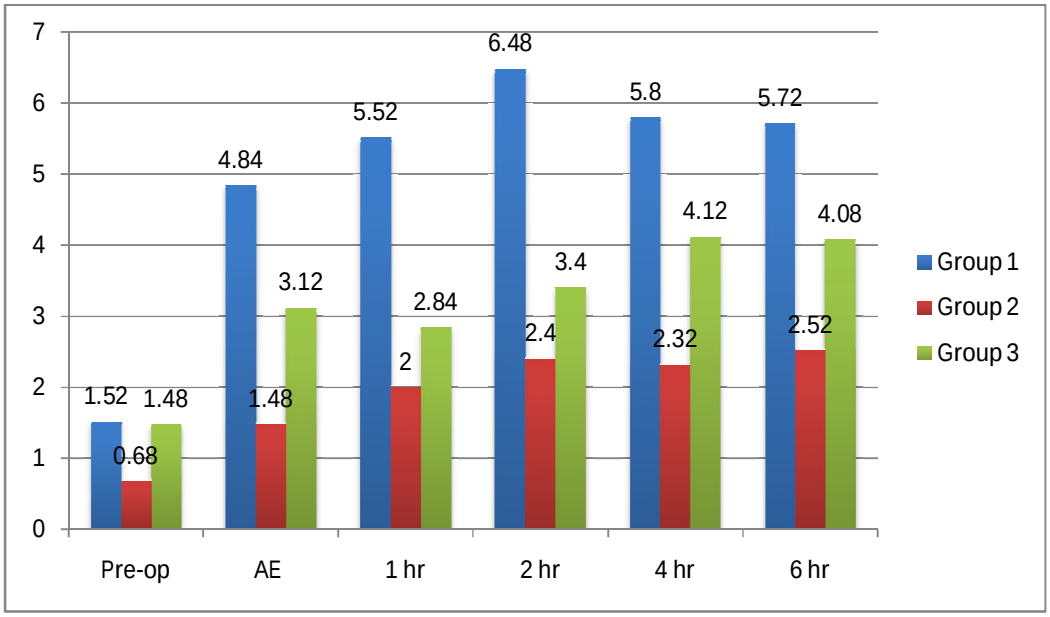

Figure 11.11 Pain scores in the three groups at different time intervals

Table 11.19 Pain scores in group 1 and group 2

VAS	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Mean difference (1-2)	P value
Pre-op	1.52 ± 0.510	0.68± 0.476	0.840	0.000#
AE	4.84± .624	1.48± .510	3.360	0.000#
1 hr	5.52± 0.510	2.00± 0.408	3.520	0.000#
2 hr	6.48± 0.510	2.40± 0.500	4.080	0.000#
4 hr	5.80± 0.408	2.32± 0.476	3.480	0.000#
6 hr	5.72 ± 0.458	2.52 ± 0.510	3.200	0.000#

- p value significant

The pain scores in group 2 is less than group 1 preoperatively, after extubation and 1, 2, 4 & 6 hours postoperatively and this difference is significant ($p<0.05$)

Table 11.20 Pain scores between group 1 and group 3

VAS	Group 1 (Mean±SD)	Group 3 (Mean±SD)	Mean difference (1-3)	P value
Pre-op	1.52 ± 0.510	1.48± 0.510	0.040	1.000
AE	4.84± 0.624	3.12 ± 0.332	1.720	0.000#
1 hr	5.52± 0.510	2.84± 0.374	2.680	0.000#
2 hr	6.48± 0.510	3.40± 0.500	3.080	0.000#
4 hr	5.80± 0.408	4.12± 0.332	1.680	0.000#
6 hr	5.72 ± 0.458	4.08± 0.277	1.640	0.000#

- p value significant

The mean pain scores in group 3 is significantly less ($p<0.05$) than group 1 after extubation and 1, 2, 4 and 6 hours postoperatively.

Table 11.21 Pain scores in group 2 and 3

VAS	Group 2 (Mean±SD)	Group 3 (Mean±SD)	Mean difference (2-3)	P value
Pre-op	0.68± 0.476	1.48± 0.510	0.800	0.000#
AE	1.48± .510	3.12 ± 0.332	1.640	0.000#
1 hr	2.00± 0.408	2.84± 0.374	0.840	0.000#
2 hr	2.40± 0.500	3.40± 0.500	1.000	0.000#
4 hr	2.32± 0.476	4.12± 0.332	1.800	0.000#
6 hr	2.52 ± 0.510	4.08± 0.277	1.560	0.000#

 # - p value significant

The pain scores in group 2 are lower than that of group 1 which is significant.

Table 11.22 Anxiety scores in the three groups

AS	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	P value
Pre-op	1.84± 0.37	0.20 ± 0.41	1.16 ± 0.37	0.000#
AE	1.72 ± 0.46	0.48± 0.51	1.16 ± 0.37	0.000#
1 hr	2.80± 0.41	0.40± 0.50	1.60± 0.50	0.000#
2 hr	3.52± 0.51	0.56± 0.51	1.96± 0.20	0.000#
4 hr	3.32± 0.48	0.60± 0.50	1.60± 0.50	0.000#
6 hr	3.32± 0.48	0.64 ± 0.49	1.64± 0.49	0.000#

- p value significant

The mean anxiety scores in group 2 is less than group 3 which is less than group 1 and this difference is statistically significant.

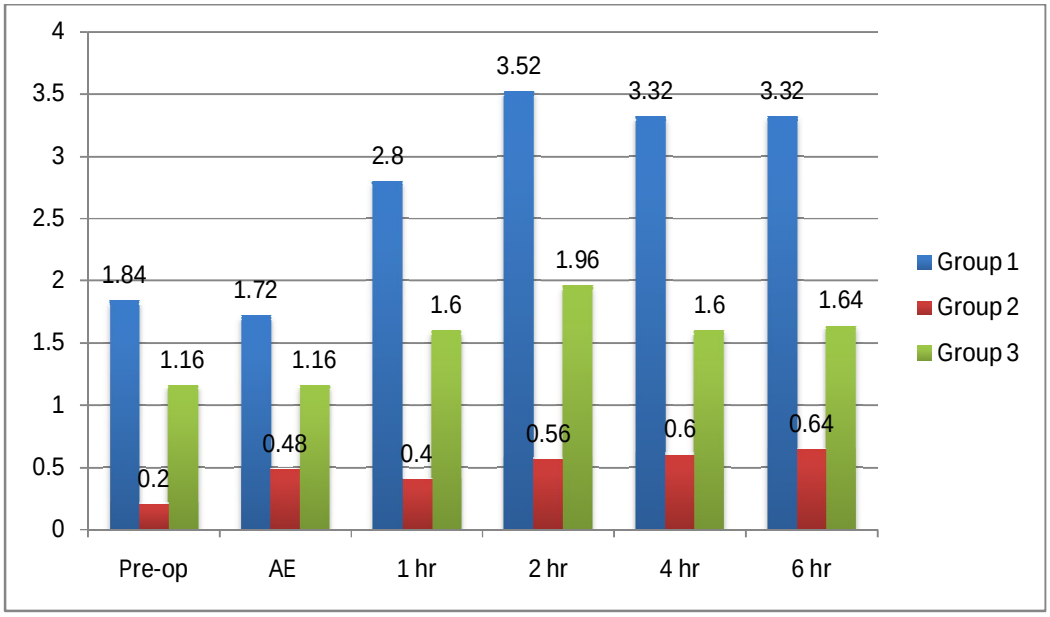

Figure 11.12 Anxiety scores in the three groups at different time intervals

Table 11.23 Anxiety scores in group 1 & 2

AS	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Mean difference (1-2)	P value
Pre-op	1.84 ± 0.37	0.20 ± 0.41	1.640	0.000#
AE	1.72 ± 0.46	0.48 ± 0.51	1.240	0.000#
1 hr	2.80 ± 0.41	0.40 ± 0.50	2.400	0.000#
2 hr	3.52 ± 0.51	0.56 ± 0.51	2.960	0.000#
4 hr	3.32 ± 0.48	0.60 ± 0.50	2.720	0.000#
6 hr	3.32 ± 0.48	0.64 ± 0.49	2.680	0.000#

- p value significant

The mean anxiety scores in group 2 is less than that of group 1 preoperatively, after extubation and 1, 2, 4 and 6 hours after extubation. This difference is statistically significant.

Table 11.24 Anxiety scores between group 1 & 3

AS	Group 1 (Mean±SD)	Group 3 (Mean±SD)	Mean difference (1-3)	P value
Pre-op	1.84± 0.37	1.16 ± 0.37	0.680	0.000#
AE	1.72 ± 0.46	1.16 ± 0.37	0.560	0.000#
1 hr	2.80± 0.41	1.60± 0.50	1.200	0.000#
2 hr	3.52± 0.510	1.96± 0.20	1.560	0.000#
4 hr	3.32± 0.48	1.60± 0.50	1.720	0.000#
6 hr	3.32± 0.48	1.64± 0.49	1.680	0.000#

- p value significant

The mean anxiety score in group 3 is lesser than that of group 1 and this difference is statistically significant.

Table 11.25 Anxiety scores between group 2 & 3

AS	Group 2 (Mean±SD)	Group 3 (Mean±SD)	Mean difference (2-3)	P value
Pre-op	0.20 ± 0.41	1.16 ± 0.37	0.960	0.000#
AE	0.48± 0.51	1.16 ± 0.37	0.680	0.000#
1 hr	0.40± 0.50	1.60± 0.50	1.200	0.000#
2 hr	0.56± 0.51	1.96± 0.20	1.400	0.000#
4 hr	0.60± 0.50	1.60± 0.50	1.000	0.000#
6 hr	0.64 ± 0.49	1.64± 0.49	1.000	0.000#

- p value significant

The mean anxiety scores in group 3 is less than that of group 1 which is statistically significant.

Table 11.26 Sedation scores in the three groups

RSS	Group 1	Group 2	Group 3	P value
Pre-op	1.00± 0.00	2.32± 0.48	1.52± 0.51	0.000#
AE	1.28 ± 0.46	2.64 ± 0.49	2.48± 0.51	0.000#
1 hr	1.48± 0.51	3.60± 0.51	3.52± 0.50	0.000#
2 hr	1.48± 0.51	3.80 ± 0.41	3.52 ± 0.51	0.000#
4 hr	1.56 ± 0.51	3.92± 0.28	3.44± 0.51	0.000#
6 hr	1.60± 0.50	3.72± 0.46	3.40± 0.50	0.000#

- p value significant

The sedation score in group 2 is greater than that of group 3 which is greater than that of group 1 preoperatively, after extubation and 1, 2, 4 and 6 hours postoperatively.

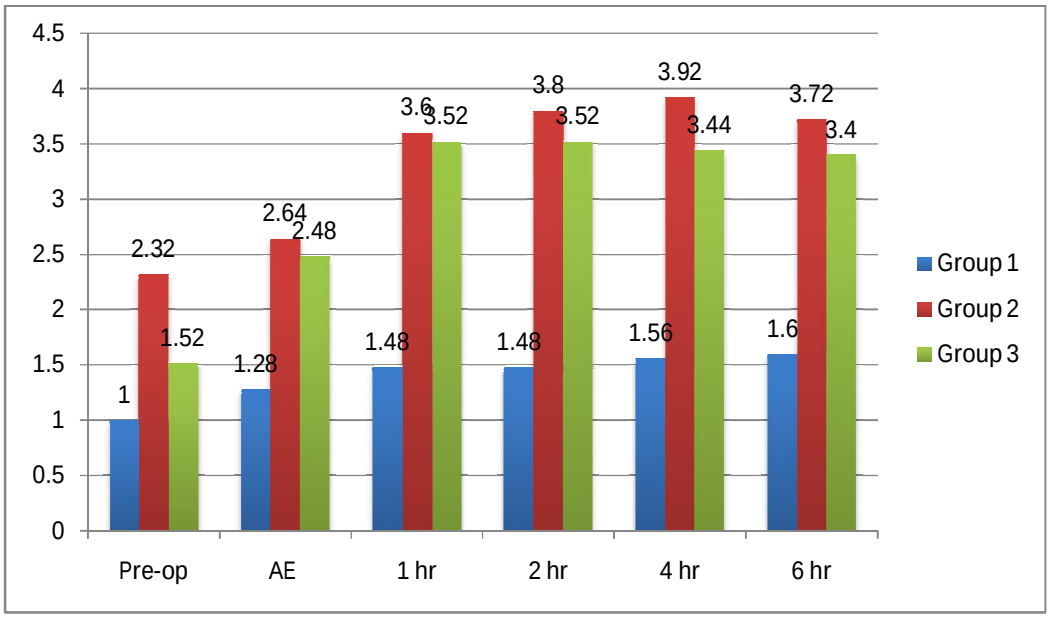

Figure 11.13 Ramsay sedation score in the three groups

Table 11.27 Sedation scores in group 1& 2

RSS	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Mean difference (1-2)	P value
Pre-op	1.00± 0.00	2.32 ± 0.48	1.320	0.000#
AE	1.28 ± 0.46	2.64 ± 0.49	1.360	0.000#
1 hr	1.48± 0.51	3.60± 0.51	2.120	0.000#
2 hr	1.48± 0.51	3.80 ± 0.41	2.320	0.000#
4 hr	1.56 ± 0.51	3.92± 0.28	2.360	0.000#
6 hr	1.60± 0.50	3.72± 0.46	2.120	0.000#

- p value significant

The sedation score in greater in group 2 than in group 1 with a statistically significant difference in all time intervals

Table 11.28 Sedation scores in group 1 & 3

RSS	Group 1 (Mean±SD)	Group 3 (Mean±SD)	Mean difference (1-3)	P value
Pre-op	1.00± 0.00	1.52 ± 0.51	0.520	0.000#
AE	1.28 ± 0.46	2.48 ± 0.51	1.200	0.000#
1 hr	1.48± 0.51	3.52± 0.50	2.040	0.000#
2 hr	1.48± 0.51	3.52 ± 0.51	2.040	0.000#
4 hr	1.56 ± 0.51	3.44± 0.51	1.880	0.000#
6 hr	1.60± 0.50	3.40± 0.50	1.800	0.000#

- p value significant

The sedation score in group 3 is significantly greater than group 1 in all the time intervals

Table 11.29 Sedation scores in group 2 & 3

RSS	Group 2 (Mean±SD)	Group 3 (Mean±SD)	Mean difference (2-3)	P value
Pre-op	2.32 ± 0.48	1.52 ± 0.51	0.800	0.000#
AE	2.64 ± 0.49	2.48 ± 0.51	0.160	0.746
1 hr	3.52± 0.51	3.60± 0.50	0.080	1.000
2 hr	2.80 ± 0.41	3.52 ± 0.51	0.720	0.000#
4 hr	2.92± 0.28	3.44± 0.51	0.520	0.000#
6 hr	2.72± 0.46	3.40± 0.50	0.680	0.000#

- p value significant

The mean sedation score in group 2 is significantly greater than that of group 3 preoperatively and 2, 4 and 6 hours postoperatively. Immediately after extubation and 1 hour after extubation sedation score in group 3 is comparable to that of group 2.

Table 11.30 Mean fentanyl requirement in the 3 groups

	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	P value
Fentanyl requirement (micrograms)	128.80±17.40	40.40 ± 9.17	60.40 ± 17.29	0.004#

- p value significant

The mean fentanyl requirement in group 1 is 128±17.40, in group 2 is 40.40±9.17 and in group 3 it is 60.40±17.29. Fentanyl requirement is more in group 1 compared to group 3, which itself is more than group 2. These differences are statistically significant.

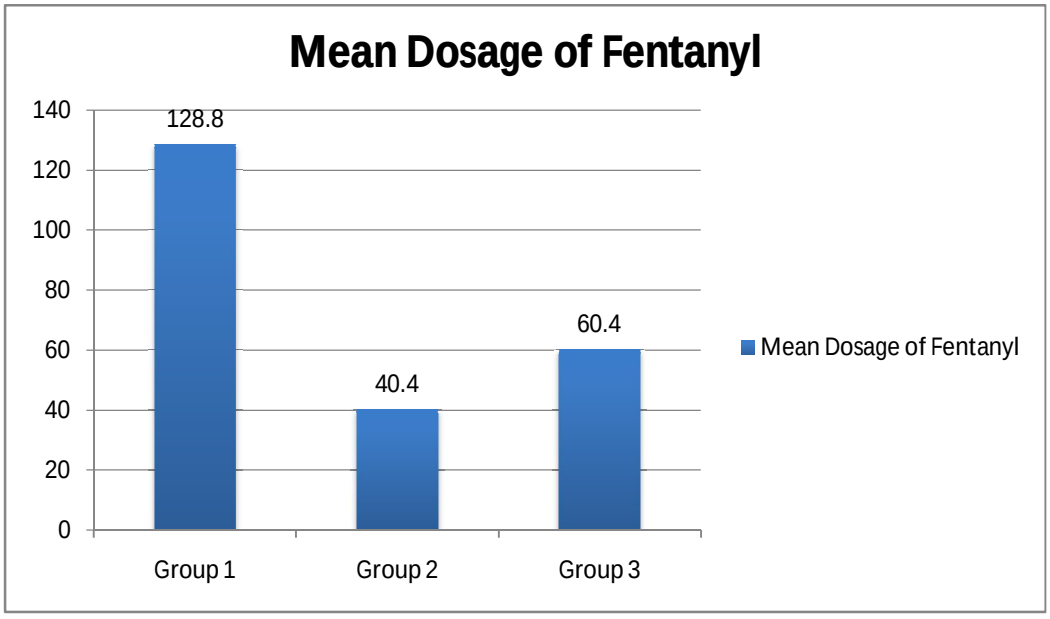

Figure 11.14 Fentanyl requirements among the three groups

Table 11.31 Adverse effects in the three groups

	Group 1 **N(%)**	**Group 2** **N (%)**	**Group 3** **N (%)**
Nausea	2 (8%)	5 (20%)	1 (4%)
Vomiting	3 (12%)	5 (20%)	1 (4%)
Drowsiness	1 (4%)	8 (32%)	1 (4%)

From the above table it is clear that the adverse effects like nausea, vomiting and drowsiness in group 3 is less than that of group 1 and group 2

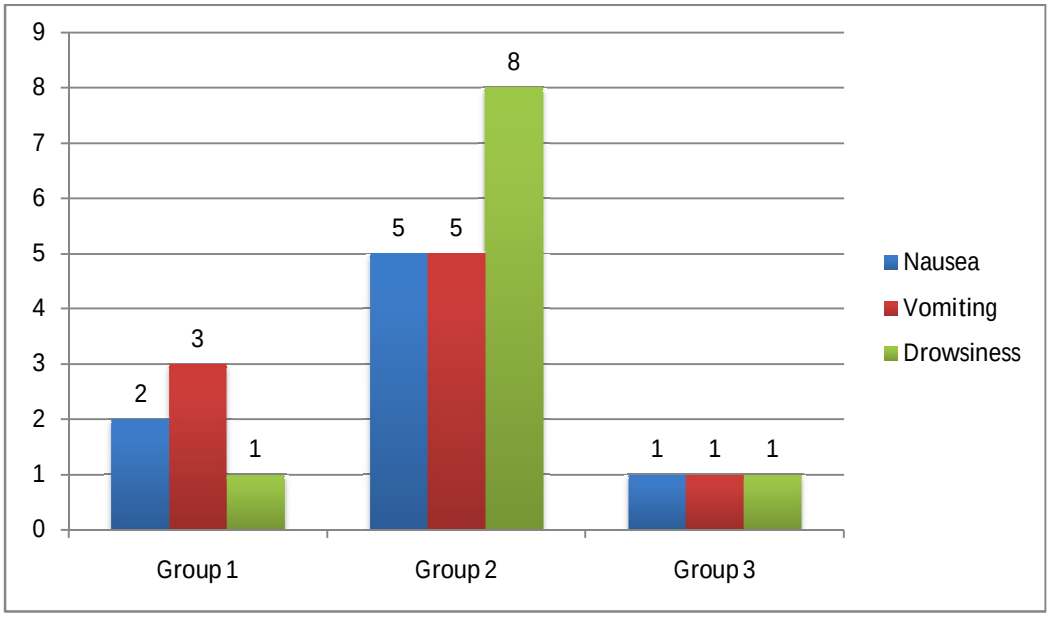

Figure 11.15 Complications among the three groups

DISCUSSION

In the present study, the pain scores of the patients who received tramadol and pregabalin were significantly decreased in comparison to placebo group. The tramadol group had the least pain scores when compared to the pregabalin and placebo groups.

It was also observed that the analgesia provided by tramadol was superior to that of pregabalin, but pregabalin was more effective in reducing the pain when compared to placebo.

The amount of rescue analgesia required was more in control group and hence the total dose of fentanyl given during the first six hours of the postoperative period was relatively more when compared to tramadol and pregabalin groups.

In a study by Pandey CK ET al.[68] fentanyl requirement is decreased in patients undergoing lumbar discectomy in gabapentin group. Similar results were obtained by Turan A et al.[89] for spinal surgeries. Pandey CK et al.[69] used 600mg gabapentin and obtained similar results. Turan An et al.[90] found a decrease in tramadol comsumption in patients who were given gabapentin for abdominal hysterectomy. In other studies by Fassoulaki A et al.[28], Jokela R et

al.[48] and Gianesello et al.[34] opioid consumption is decreased as with above studies.

Hence, the opioid sparing effect of pregabalin as per my study is in agreement with the above studies.[68, 89, 69, 90, 28, and 35]

Pregabalin has previously been shown to have good analgesic efficacy in patients with postherpetic neuralgia[1], spinal cord injury[92], gynaecological surgery[48], dental surgery[43] and in patients following lumbar laminectomy and discectomy[67]. However, the doses in these studies varied from 75 mg to 300 mg per day.

In this study, the anxiety scores in pregabalin and tramadol groups were significantly lower when compared to the placebo group. However, the anxiety scores were significantly lower in the pregabalin group in comparison to the placebo group, whereas it is significantly higher than the tramadol group. This observation shows that pregabalin also has an anxiolytic effect additionally, although it is to a lesser extent when compared to tramadol.

Ozgencil E et al.[67] in their study found that pregabalin 300 mg per day and gabapentin 1200 mg per day had more analgesic, anxiolytic and also opioid sparing effects. Patient satisfaction is also high and is also more effective in preventing postoperative shivering than the placebo following lumbar laminectomy and discectomy.

Menigaux C et al[62] in their study concluded that premedication with gabapentin 1200mg improved preoperative anxiolysis, postoperative analgesia and early knee mobilization after arthroscopic anterior cruciate ligament repair.

The above two studies[67,62] show the anxiolytic effect of pregabalin which is in line with my study.

The preoperative sedation scores in my study were significantly greater in tramadol group when compared to the pregabalin and placebo groups. After extubation and postoperatively the level of sedation increased in both pregabalin and tramadol. However, this increase in sedation in pregabalin group was more after extubation and 1 hour postoperatively (but less than tramadol insignificantly) ; rest all the time intervals it was significantly lower than the tramadol group though the sedation was significantly higher than the placebo group.

From this, we infer that pregabalin has a good anxiolytic effect without resulting in excessive sedation.

Yoon MH et al.[102] in their animal study, administered gabapentin intrathecally to rats. In their study they concluded that spinally delivered gabapentin has no effect on resting heart rate or blood pressure. But it attenuated the enhanced pain behaviour and cardiovascular response otherwise produced by the injury.

Van Den Berg AA et al.[95] studied the obtundation of stress response to laryngoscopy and intubation by opioids. In this study they found that the increase in heart rate (1 minute after intubation) that occurred with laryngoscopy and intubation is not attenuated by tramadol but rather it returned at a faster rate to baseline in tramadol group (5 minutes after intubation) when compared to placebo group (7 minutes after intubation).

In my study, the increase in heart rate is significantly lower in tramadol group while compared to placebo at 1 and 3 minutes after intubation and at 30, 60 and 120 minutes and after extubation. The decrease in heart rate is insignificant preoperatively and 5 minutes after intubation.

Similarly in the pregabalin group, the increase in heart rate is significantly lower at 1 & 3 minutes after intubation, at 30, 60 & 120 minutes and after extubation when compared to the placebo group.

The systolic blood pressure, diastolic blood pressure and mean arterial blood pressure in the tramadol group is significantly lower when compared to placebo group at 1 & 3 minutes after intubation and after extubation. In pregabalin group the systolic, diastolic and mean arterial blood pressure are significantly lower at 1 minute after intubation and after extubation.

Thus both pregabalin and tramadol given preoperatively, apart from preventing pressor response to laryngoscopy and intubation also helps to maintain a stable hemodynamics throughout surgery.

Drowsiness was less frequent in the pregabalin group (4%) compared to the tramadol group (32%). Fewer patients had nausea (4%) and vomiting (4%) with pregabalin when compared to placebo (nausea 8%, vomiting 12%) and tramadol (nausea 20%, vomiting 20%). This implies that the incidence of nausea and vomiting is more with tramadol and placebo than with pregabalin.

Edwards JE et al.[27]studied the efficacy of oral tramadol and tramadol with acetaminophen combination for acute postoperative pain. According to their study the adverse effects with tramadol were dizziness, drowsiness, nausea, vomiting and headache.

Moore RA et al.[65] did a meta-analysis to assess the safety and efficacy of oral tramadol when compared with standard analgesics. They found that the adverse effects with tramadol were greater at higher doses due to dose-response effect.

In a study by Ozgencil et al.[67] it was found that pregabalin is well tolerated at all doses and has higher patient satisfaction.

All these studies[67,27,74] are in agreement with my study regarding the adverse effects of pregabalin and tramadol.

SUMMARY

This prospective, randomised, single blinded placebo-controlled study evaluated the efficacy of preoperative administration of pregabalin and tramadol for postoperative pain management in patients undergoing lumbar laminectomy.

Seventy five patients belonging to ASA1 and 2, between 20 to 60 years of either sex, satisfying inclusion criteria were randomised into three groups containing 25 patients each.

Group 1– placebo

Group 2 – tramadol

Group 3 – pregabalin

These drugs were administered to the patients 1 hour before anaesthetic induction. The heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure were recorded preoperatively(baseline and 1 hour after drug administration), intraoperatively and postoperatively. Respiratory rate and saturation were also recorded preoperatively and postoperatively. Pain scores, anxiety scores, sedation scores were recorded 1 hour after drug administration, after extubation and postoperatively. Fentanyl

consumption in the postoperative period and any adverse effects were also noted. The data was analysed using SPSS software version 20. The demographic profiles of the three groups were matched and the baseline hemodynamic variables in all three groups were comparable.

The pain scores and anxiety scores were significantly reduced in pregabalin and tramadol groups when compared to the placebo group but the reduction in scores in the pregabalin group is significantly less than that of the tramadol group. The sedation score is higher in tramadol group when compared to placebo and pregabalin; however, there was no significant difference in sedation between pregabalin and tramadol immediately after extubation and at 1 hour postoperatively. The sedation scores remained significantly higher in the pregabalin group when compared to the placebo group.

Further the systolic, diastolic and mean arterial blood pressures were significantly lower in the tramadol group when compared to the placebo group at 1 & 3 minute after intubation and after extubation whereas in pregabalin group these parameters were significantly lower than placebo group at 1 minute after intubation and after extubation. Heart rate changes in tramadol and pregabalin groups were significantly lower than the placebo group at 1 & 3 minutes after intubation and at 30, 60 and 120 minutes and after extubation.

The mean requirement of fentanyl is significantly lower in pregabalin and tramadol groups when compared to placebo group. Side effects in tramadol and placebo group were significantly higher than the pregabalin group.

CONCLUSION

The following conclusions can be drawn from the study.

Pregabalin has a statistically significant effect when compared to placebo, but this effect is less when compared to tramadol.

The need for rescue analgesia is least in tramadol patients followed by pregabalin and it increases maximum in the placebo group.

Pregabalin has a statistically significant anxiolytic effect when compared to the placebo group.

The anxiolytic effect of pregabalin is associated with less sedation when compared to that of tramadol.

Pregaalin reduces the pressor response to laryngoscopy and intubation and also maintains a stable hemodynamics similar to tramadol.

Pregabalin has lowest number of postoperative complications like nausea, vomiting and drowsiness when compared to tramadol.

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INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. V. Reena Sanges

Postgraduate MD (Anaesthesia),
Madras Medical College,
Chennai – 600 003.

Dear Dr. V. Reena Sanges

The Institutional Ethics Committee has considered your request and approved your study titled **"A Prospective randomized placebo - controlled study evaluating the effectiveness of oral Pregabalin and Tramadol for post operative pain management in patients undergoing lumbar laminectomy."** **No.**24082014.

The following members of Ethics Committee were present in the meeting held on 05.08.2014 conducted at Madras Medical College, Chennai-3.

1. Dr.C.Rajendran, M.D.,	: Chairperson
2. Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandhini, M.D., Inst.of Pharmacology, MMC	: Member
5. Dr.G.Muralidharan, Director Incharge, Inst.of Surgery	: Member
6. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
7. Prof.Tito, M.D., Director i/c, Inst.of Internal Medicine, MMC	: Member
8. Thiru S.Rameshkumar, Administrative Officer	: Lay Person
9. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
10. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

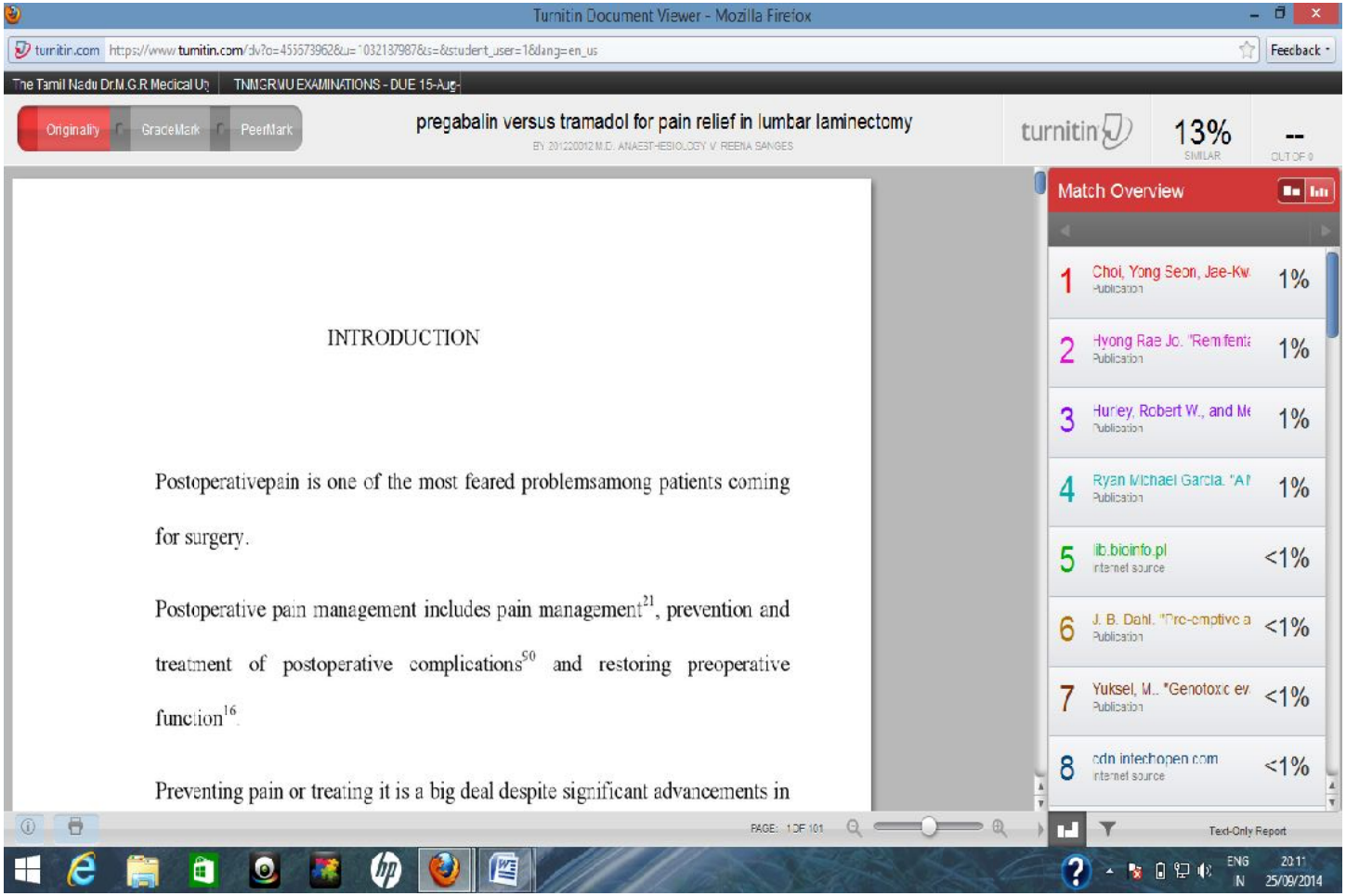
We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003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INTRODUCTION
Postoperativepain is one of the most feared problemsamong patients coming for surgery.
Postoperative pain management includes pain management[21], prevention and treatment of postoperative complications[50] and restoring preoperative function[16].
Preventing pain or treating it is a big deal despite significant advancements in
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PATIENT CONSENT FORM

Study title: "A Prospective, randomized, placebo-controlled study evaluating the effectiveness of oral pregabalin and tramadol for postoperative pain management in patients undergoing lumbar laminectomy".

Study centre: INSTITUTE OF ANAESTHESIOLOGY AND CRITICAL CARE , MADRAS MEDICAL COLLEGE & GOVT GENERAL HOSPITAL, CHENNAI 600003.

Participant name: Age: Sex: I.P.no:

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the pitfall in the procedure. I have been explained about the safety, advantage and disadvantage of the technique.

I understand that my participation in the study is voluntary and that I am free to withdraw at anytime without giving any reason.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

Date: Signature / thumb impression of patient:

Place: Patient name:

Signature of the investigator:

Name of the investigator:

PROFORMA

NAME: DATE:

AGE/SEX: IP.NO:

SPINAL LEVELS: GROUP:

DURATION OF SURGERY: ASA:

Ht: cms MMS:

Wt: kgs

PRE OP ASSESSMENT:

HISTORY: H/O Co-morbid illness

H/O Allergy

H/O any medications

PREMEDICATION:

Pregabalin/ Tramadol/ Placebo: TIME:

INDUCTION TIME:

SKIN INCISION TIME:

SKIN CLOSURE TIME:

PARAMETERS	BL	PREOP	AI-1 MIN	AI-3 MIN	AI-5 MIN	30 MIN	60 MIN	120 MIN
HR /min								
SBP mmHg								
DBP mmHg								
MAP mmHg								

PARAMETERS	PREOP	AE	1 HR	2 HR	4 HR	6 HR
VAS score						
Anxiety score						
Sedation score						

POSTOPERATIVE FENTANYL CONSUMPTION (micrograms):

ADVERSE EFFECTS: nausea/ vomiting/ drowsiness:

MASTER CHART

S.NO	NAME	AGE	SEX	Wt.[KG]	Ht.[mts]	BMI[KG/M2]	GROUP	ASA	BASELINE PARAMETERS				DURATION	SPINAL LEVELS
									HR	SBP	DBP	MAP		
1	USHA	35	F	50	1.52	22.22	1	1	72	116	68	84	150	2
2	BANUMATHI	37	F	45	1.5	20	1	2	72	140	86	104	140	1
3	ANJALAI	48	F	60	1.53	25.63	1	2	80	136	88	104	130	2
4	VALLI	43	F	48	1.51	21	1	1	78	134	81	98	140	1
5	GOPALAKRISHNAN	44	M	67	1.65	24.6	1	2	74	110	70	83	120	2
6	THANGARAJ	49	M	68	1.66	24.6	1	1	86	126	80	95	160	1
7	KUPPU	39	F	65	1.58	26.43	1	2	71	120	78	91	130	1
8	CHINNAKULANTHAI	46	F	52	1.5	23.11	1	1	70	124	82	95	150	2
9	DURAI	45	M	56	1.67	20	1	2	76	110	71	83	140	1
10	MALLIGA	48	F	52	1.5	23.11	1	1	76	124	83	96	140	2
19	VIJI	43	F	51	1.51	22.36	1	1	79	120	70	86	140	1
20	LAKSHMI	52	F	50	1.54	21	1	1	68	106	71	82	150	2
21	PITCHAIKANNI	40	M	56	1.5	24.8	1	1	76	132	78	95	160	1
22	SANDHYA	32	F	50	1.45	23.78	1	1	82	140	82	101	150	2
23	POOVAN	54	M	65	1.65	23.87	1	2	75	142	84	103	180	2
24	SUMITHA	58	F	50	1.5	22.22	1	2	71	118	72	87	140	1
25	SELVI	60	F	55	1.69	22.6	1	2	78	128	82	97	150	2
26	KRISHNAVENI	46	F	50	1.52	22.22	2	1	65	120	74	89	150	1
27	GOVINDHASAMY	54	M	45	1.5	20	2	2	82	132	81	97	140	1
28	JAYANTHI	56	F	60	1.53	25.63	2	2	71	113	69	83	120	2
29	DEVAKI	60	F	48	1.51	21	2	1	72	120	70	86	140	2
30	MENAKA	58	F	67	1.65	24.6	2	2	69	112	70	83	150	1
31	ANBALAGAN	36	M	56	1.55	23.3	2	1	66	130	84	99	140	1
32	VIGNESH	37	M	48	1.53	20.5	2	2	83	142	91	107	120	1
33	SAMPATH	32	M	68	1.66	24.6	2	1	72	123	79	93	150	2
34	NASREEN	56	F	54	1.56	22.1	2	1	73	130	80	96	140	2
35	LALITHA KUMARI	44	F	63	1.67	22.58	2	2	70	122	80	93	130	2
36	SHEELA DEVI	45	F	46	1.48	21	2	1	84	110	64	79	140	2
37	NIRMALA	48	F	59	1.52	25.5	2	2	68	122	71	87	120	1
38	ROSEMARY	42	F	56	1.49	25.22	2	2	86	110	59	75	120	2
39	SELVARAJ	40	M	68	1.64	25.2	2	1	76	110	60	76	150	1
40	BALAMMAL	39	F	65	1.58	26	2	1	86	120	80	93	150	1
41	RAMAMOORTHY	45	M	52	1.5	23.11	2	2	76	102	72	81	140	1
42	GNANASUNDARI	56	F	66	1.64	25.2	2	2	60	132	78	95	140	1
43	INBALAKSHMI	33	F	53	1.55	22	2	1	73	114	66	81	150	2
44	KASILINGAM	36	M	66	1.58	26.43	2	1	68	128	68	87	160	2
45	GANAPATHY	39	M	57	1.53	24.34	2	1	71	120	68	85	150	2
46	CHANDRAKUMARI	40	F	69	1.68	24.44	2	2	64	128	86	99	130	1
47	SUGANTHI	49	F	61	1.63	22.95	2	2	68	120	93	101	140	2
48	ESWARI	38	F	58	1.66	21	2	1	80	112	82	91	130	2
49	PARVATHY	32	F	56	1.67	20	2	2	68	112	82	91	130	2
50	JANAKIRAM	42	M	50	1.54	21	2	1	70	122	66	84	140	2
51	SENGINI	33	M	53	1.5	23.55	3	1	84	136	78	97	150	2
52	BABU	45	M	46	1.49	20.7	3	2	76	140	77	98	150	1
53	MURUGESAN	38	M	49	1.46	22.9	3	1	68	117	83	94	120	2
54	SAROJA	60	F	52	1.51	22.8	3	2	70	110	76	87	120	1
55	SHANTHINI	44	F	55	1.55	24.44	3	1	86	129	91	102	150	2
56	JAYARAM	52	M	52	1.48	23.73	3	1	78	124	80	94	140	1
57	PACHAMUTHU	49	M	56	1.56	23	3	2	76	119	77	91	150	2
58	RAMANUJAM	58	M	51	1.51	22.36	3	1	76	114	75	88	140	1
59	NAGAMMAL	50	F	65	1.66	23.58	3	2	86	123	86	98	150	1
60	SOLIAMMAL	52	F	58	1.55	24.14	3	1	84	116	74	88	130	2
61	SIVARAMAN	40	M	59	1.63	22.2	3	2	76	132	80	97	160	1
62	SABBOO	44	F	52	1.52	22.5	3	2	70	122	82	95	150	1
63	AMUDHA	37	F	56	1.57	22.7	3	2	60	126	84	98	150	1
64	AMEER BASHA	58	M	60	1.68	21.25	3	2	74	130	80	96	150	1
65	VIJAYLAKSHMI	55	F	53	1.54	22.34	3	1	73	130	78	95	180	2
66	MEENA	57	F	68	1.72	22.9	3	2	74	124	78	93	140	2
67	MENAKA	43	F	66	1.75	21.55	3	2	68	108	70	82	140	1
68	MARUTHAYE	44	F	50	1.6	19.5	3	2	76	110	76	87	160	2
69	KANNIAMMAL	42	F	56	1.58	22.4	3	1	71	121	78	92	180	1
70	CHARU	46	F	60	1.68	21.25	3	2	78	129	84	99	140	1
71	SRIVIDHYA	38	F	53	1.54	22.34	3	1	64	130	82	98	180	2
72	JANAKI	32	F	68	1.72	22.9	3	2	70	126	84	98	150	2
73	MADHU	38	F	66	1.75	21.55	3	1	68	122	81	94	140	1
74	SUBHA	36	F	56	1.58	22.4	3	1	71	116	68	84	120	2
75	VISALAKSHI	58	F	62	1.6	24.21	3	1	80	112	71	84	120	2

HEART RATE								SYSTOLIC BLOOD PRESSURE							
PREOP	AI 1MIN	AI 3 MIN	AI 5MIN	3OMIN	60 MIN	120 MIN	AE	PREOP	AI-1MIN	AI-3MIN	AI- 5MIN	30 MIN	60 MIN	120 MIN	AE
83	84	88	82	78	76	78	95	116	142	118	116	120	118	120	139
80	82	82	76	76	74	76	91	140	134	119	109	142	140	142	133
86	92	102	98	84	82	84	102	136	162	131	116	124	122	124	148
92	92	88	82	80	82	80	96	134	199	149	117	117	115	117	186
79	84	81	76	76	78	76	92	110	133	125	122	95	93	95	142
92	89	92	80	90	92	90	108	126	162	135	126	119	121	119	158
74	79	72	74	76	74	76	88	120	128	112	116	116	118	116	121
74	79	71	76	80	82	80	94	124	142	128	118	116	118	116	139
78	82	86	82	80	82	80	88	110	102	101	92	90	92	90	101
78	74	86	92	78	80	78	94	124	144	124	162	112	114	112	139
85	86	82	74	72	74	72	99	120	171	141	118	112	114	112	162
74	75	84	76	88	90	88	92	106	109	111	118	102	104	102	105
82	86	85	71	86	88	86	96	132	163	131	141	99	101	99	157
84	81	98	87	85	87	85	109	140	165	111	121	110	112	110	152
79	78	92	86	75	77	75	110	142	169	158	131	127	129	127	171
75	80	98	89	88	90	88	112	118	167	139	127	116	118	116	159
84	88	89	77	86	84	86	101	128	151	119	121	130	132	130	148
71	85	73	71	68	66	62	86	110	128	120	121	122	124	118	110
79	113	99	87	80	82	80	107	129	136	126	136	130	132	128	120
77	87	87	73	70	72	70	84	117	120	116	118	117	118	112	100
71	81	74	71	74	70	72	81	118	126	117	118	122	120	124	122
73	85	76	73	74	72	70	85	114	112	114	120	114	116	112	110
72	89	74	70	68	66	64	83	120	138	130	136	132	134	128	120
80	92	89	80	80	82	80	88	139	146	136	146	140	142	138	130
78	80	80	74	72	70	72	80	137	130	126	128	127	128	122	132
72	82	78	70	70	71	70	78	128	136	127	128	122	136	134	132
74	84	80	72	73	72	70	81	124	122	124	130	124	126	122	136
89	102	81	82	78	80	81	88	100	118	110	116	112	112	108	100
74	83	71	72	70	71	70	82	119	126	116	126	120	122	118	100
92	93	88	89	82	80	82	90	114	117	114	114	110	114	110	118
82	84	78	74	74	73	72	80	108	116	107	108	112	110	110	112
92	112	96	88	88	84	85	100	110	128	120	126	122	124	118	110
81	93	86	88	74	73	74	92	104	102	104	110	104	106	103	100
74	92	78	62	62	60	60	90	130	130	128	132	128	131	126	122
78	85	70	72	70	68	71	84	115	113	112	122	115	114	110	112
71	82	74	76	68	64	66	80	131	136	128	134	130	132	126	118
76	94	96	81	72	70	70	90	125	128	122	126	124	122	120	128
71	84	79	71	65	64	64	80	126	134	124	126	120	134	132	136
79	106	95	88	66	64	65	90	122	120	122	128	122	124	120	118
88	103	90	75	78	74	75	92	116	120	116	116	112	116	112	120
78	84	80	71	66	62	60	80	110	114	108	110	114	112	116	114
80	88	82	75	72	74	68	84	112	130	122	128	124	126	120	112
89	89	81	82	84	85	87	102	119	147	125	119	128	126	128	139
84	86	79	72	78	80	82	90	122	109	97	112	99	101	103	106
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86	84	80	76	88	90	82	92	112	156	110	101	100	102	105	148
92	94	96	88	83	81	83	112	122	164	159	133	111	109	111	159
94	89	94	92	74	72	73	92	109	124	121	117	101	103	105	126
81	84	86	88	70	68	70	93	132	136	112	114	127	129	131	138
76	79	77	74	64	62	63	88	116	126	101	103	99	101	103	126
64	72	78	62	76	78	80	92	129	147	131	141	120	122	125	132
79	82	88	86	70	72	73	86	128	148	124	119	123	125	127	148
78	82	70	72	70	68	69	85	133	147	127	124	124	122	124	151
80	86	74	76	68	70	71	92	121	134	110	112	118	116	118	127
71	76	74	76	80	82	81	82	110	114	101	108	103	105	107	110
74	78	75	76	73	71	73	80	110	119	102	101	108	110	112	114
76	80	96	81	80	82	84	94	112	128	114	120	111	113	115	126
82	87	84	80	66	68	70	97	126	136	118	126	121	123	125	138
71	76	79	71	74	76	74	84	128	142	110	114	118	120	122	133
75	79	78	69	70	72	74	91	128	132	129	118	119	121	123	128
79	82	95	88	70	72	74	106	118	158	149	132	121	123	125	165
78	81	83	74	83	85	87	95	112	127	102	110	108	110	112	129
88	82	90	75	84	86	88	103	116	107	117	121	102	105	107	108

DIASTOLIC BLOOD PRESSURE								MEAN ARTERIAL PRESSURE							
PREOP	AI-1 MIN	AI- 3MIN	AI- 5 MIN	30 MIN	60 MIN	120MIN	AE	PREOP	AI- 1 MIN	AI-3 MIN	AI-5 MIN	30 MIN	60 MIN	120 MIN	AE
76	101	82	76	77	75	77	99	89	114	94	89	91	89	91	112
80	78	67	72	87	89	87	74	97	96	78	81	107	105	105	93
86	120	96	81	86	88	86	108	98	134	107	92	98	99	98	121
66	115	92	81	75	77	75	108	77	164	111	91	86	89	88	134
77	103	95	89	65	67	65	102	84	111	103	99	72	75	74	115
88	116	98	86	77	79	77	113	97	131	109	97	89	92	90	128
71	86	71	70	76	78	76	82	86	100	84	85	89	91	89	95
82	98	84	78	74	76	74	89	95	112	98	91	88	89	87	105
62	69	66	63	54	56	54	68	74	80	78	73	66	67	65	79
69	80	78	113	70	72	70	82	85	101	93	126	84	85	83	101
70	108	87	79	62	64	62	19	87	129	105	92	78	80	78	126
69	80	77	81	65	67	65	79	83	89	88	93	77	79	77	87
74	102	87	90	63	65	63	99	92	122	101	107	75	76	74	118
71	92	74	78	69	71	69	94	86	116	86	92	82	84	82	114
84	106	92	87	80	82	80	105	102	127	114	101	95	97	95	127
71	111	94	86	72	74	72	110	86	129	109	99	86	88	86	126
82	96	78	83	76	78	76	93	96	114	91	95	94	95	93	111
77	101	82	82	72	74	76	72	87	109	94	94	88	90	89	84
82	105	92	84	80	82	78	84	97	115	103	101	96	98	94	95
71	84	72	76	70	72	68	77	86	95	86	89	85	87	82	84
72	79	72	74	68	70	66	79	87	94	86	88	85	86	85	93
74	72	80	84	72	74	70	80	87	85	91	95	85	87	83	89
87	91	92	92	82	84	80	82	97	106	104	106	98	100	95	94
92	95	102	94	90	92	88	94	107	111	113	111	106	108	104	105
81	94	82	80	80	82	78	87	99	105	96	95	95	97	92	101
82	89	82	82	78	80	76	89	97	104	96	97	92	98	95	103
84	82	80	84	82	84	80	90	97	95	94	99	95	97	93	105
61	71	70	72	62	64	60	62	73	86	83	86	78	79	75	74
72	75	82	74	70	72	68	74	87	91	93	91	86	88	84	82
61	74	62	66	60	62	58	67	78	88	79	81	76	79	75	83
62	69	62	64	58	60	56	69	77	84	76	78	75	76	73	83
77	62	70	74	62	64	60	70	87	83	86	91	81	83	79	83
75	95	80	80	70	72	68	70	84	97	87	89	81	83	79	79
80	95	90	82	78	80	76	82	96	106	102	98	94	96	92	95
68	81	70	72	68	70	66	75	83	91	83	88	83	84	80	87
70	76	70	72	66	68	64	76	90	95	89	92	87	89	84	89
72	70	78	82	70	72	68	78	89	89	92	96	87	88	85	94
88	92	95	95	86	86	88	86	100	105	104	105	97	101	102	102
94	96	104	96	92	94	90	96	103	103	109	106	101	103	99	103
84	96	84	82	82	84	80	90	94	103	94	93	91	94	90	99
84	91	84	80	80	82	78	92	92	98	91	89	91	91	90	99
64	70	68	70	64	66	70	76	79	89	85	89	83	85	86	87
76	93	70	69	74	72	74	91	90	111	88	85	92	89	91	107
83	72	62	74	62	60	62	67	95	84	73	86	74	73	75	80
67	83	96	94	66	64	66	81	79	96	109	108	75	73	75	92
74	91	65	66	77	75	77	90	86	101	75	75	87	86	88	99
90	101	72	81	85	83	85	97	102	116	81	89	96	99	101	113
74	107	74	76	68	70	68	103	87	121	85	87	79	80	80	116
75	79	48	83	72	70	72	76	89	74	60	90	85	83	85	92
76	108	81	67	65	67	65	99	88	124	91	78	77	78	78	115
86	107	102	93	75	77	75	104	98	126	121	106	87	87	86	122
72	83	68	72	63	65	63	86	84	96	82	82	75	77	76	99
82	96	79	76	76	78	76	94	989	109	90	88	93	94	94	108
74	94	79	78	68	70	68	93	88	104	86	86	78	80	79	105
84	96	92	88	70	72	70	92	99	113	105	105	86	88	88	105
79	95	80	78	63	65	63	92	95	112	95	92	83	84	84	110
78	98	84	82	74	76	74	96	96	114	98	96	90	91	90	114
76	89	71	74	74	76	74	86	91	104	84	86	88	89	88	99
68	78	68	70	67	69	67	74	82	90	79	82	79	80	80	86
72	78	73	68	72	74	72	65	84	91	82	79	84	85	85	81
78	90	78	76	73	75	73	90	89	102	90	70	85	87	86	102
82	94	74	76	72	74	72	93	96	108	88	92	88	90	89	108
84	92	68	74	71	73	71	94	98	108	82	87	86	88	87	107
84	88	84	80	78	80	78	86	98	102	99	92	91	93	92	100
77	103	90	81	70	72	70	101	90	121	109	98	87	88	88	122
71	90	58	72	64	66	64	84	84	102	72	84	78	80	79	99
74	69	73	72	61	63	61	67	88	81	87	88	74	76	76	80

VISUAL ANALOG SCORE						ANXIETY SCORE						RAMSAY SEDATION SCORE					
PREOP	AE	1 HR	2 HR	4 HR	6 HR	PREOP	AE	1 HR	2 HR	4 HR	6 HR	PREOP	AE	1 HR	2 HR	4 HR	6 HR
2	5	6	6	5	6	2	2	3	3	3	3	1	1	1	1	2	2
2	5	6	7	6	5	2	1	2	3	3	3	1	2	2	2	1	1
1	4	5	6	6	6	1	1	3	4	4	4	1	1	2	1	1	2
2	4	5	6	6	6	2	2	3	3	3	3	1	1	1	2	1	1
1	5	6	7	6	6	2	2	3	4	3	3	1	1	2	1	2	2
1	5	5	6	5	5	2	2	2	3	3	3	1	1	1	2	1	1
1	5	5	7	6	6	1	1	3	4	4	4	1	2	2	1	2	2
2	6	6	7	6	5	2	2	3	3	3	4	1	2	1	2	2	1
2	5	5	6	6	6	2	2	3	4	3	3	1	1	1	1	2	2
2	5	5	7	6	6	2	2	3	3	3	3	1	1	2	2	2	1
1	3	5	6	6	6	2	1	3	4	3	3	1	1	1	1	2	2
1	5	6	7	6	5	2	2	3	3	3	3	1	1	2	1	2	2
2	5	6	6	6	6	2	2	3	4	4	3	1	1	1	1	2	1
1	5	6	7	6	6	2	2	3	4	4	4	1	1	1	1	2	2
2	5	6	6	6	6	2	2	3	4	3	3	1	1	1	2	1	2
1	5	6	7	6	6	2	2	2	4	4	3	1	2	2	2	1	2
1	5	6	7	6	6	2	2	3	4	4	4	1	1	1	2	1	1
0	1	2	3	2	3	0	0	0	1	0	1	2	3	3	3	3	3
0	1	2	2	3	3	0	0	0	1	1	1	2	3	4	3	3	3
1	2	2	3	2	2	0	0	0	1	1	0	3	2	4	2	3	2
1	1	2	3	3	3	0	0	0	0	0	1	2	2	3	3	3	3
1	2	2	2	2	2	1	1	0	1	0	1	2	3	4	3	3	3
1	1	2	2	2	3	0	1	1	0	0	0	2	2	3	3	3	3
1	2	2	3	3	2	1	0	1	1	1	1	2	3	4	3	3	3
0	1	2	2	2	3	0	1	0	1	0	0	2	2	3	3	3	2
1	2	2	2	2	2	1	0	1	0	0	0	2	3	4	3	2	3
0	1	2	2	2	3	0	0	0	1	1	1	2	3	4	3	3	3
0	2	2	2	2	3	1	1	0	0	1	0	3	3	3	2	3	3
1	1	2	2	3	3	1	1	1	0	0	1	2	2	3	3	3	3
1	2	2	3	2	3	0	1	1	1	1	1	2	3	4	2	3	2
0	1	2	2	2	2	0	0	0	1	1	1	3	3	3	3	3	3
0	2	1	2	2	3	0	0	1	1	1	0	3	2	4	3	3	2
0	2	1	3	3	2	0	1	0	1	1	1	2	3	3	2	2	2
1	1	3	3	3	3	0	0	0	1	1	1	3	3	4	3	3	3
1	2	3	2	2	3	0	1	1	0	1	0	2	2	4	3	3	2
1	2	2	2	2	3	0	0	0	1	1	1	2	3	3	3	3	3
1	1	2	3	3	2	0	0	0	0	1	0	3	3	3	3	3	3
1	1	2	2	2	2	0	1	0	0	0	0	2	3	3	3	3	3
1	1	2	2	2	2	0	1	1	0	1	1	2	3	4	3	3	3
1	2	2	3	3	2	0	1	1	0	0	1	3	2	4	3	3	3
1	1	2	2	2	2	0	1	1	0	1	1	3	2	4	3	3	3
1	2	2	3	2	2	0	0	0	1	0	1	2	3	3	2	3	2
1	3	3	3	4	4	1	1	2	2	1	2	1	2	4	3	3	3
2	3	3	3	4	4	1	1	1	2	2	2	2	3	3	4	4	4
1	3	3	3	4	4	1	1	2	2	2	1	1	2	4	3	3	3
2	3	3	3	4	4	2	1	1	2	2	1	2	2	4	3	4	4
1	3	2	3	4	4	1	1	2	2	1	2	1	2	4	3	3	3
2	3	3	4	4	4	2	2	2	2	2	1	1	2	4	4	3	4
1	3	3	3	4	4	2	1	1	2	2	2	1	2	3	3	4	3
2	3	2	4	4	5	1	2	1	2	1	1	2	3	4	4	3	4
1	3	3	3	4	4	1	1	2	2	2	2	1	3	4	3	4	3
2	4	3	4	4	4	1	1	1	2	1	2	1	2	3	4	3	4
1	4	3	3	4	4	1	1	2	2	2	1	2	3	4	3	4	3
2	3	3	4	4	4	1	2	1	2	1	2	2	2	3	4	3	3
1	4	3	4	4	4	1	1	1	2	2	2	2	3	4	3	4	4
1	3	2	4	5	4	1	1	2	2	1	2	2	3	4	4	3	3
2	3	3	3	4	5	1	1	1	2	1	1	2	2	4	4	4	3
2	3	3	4	5	4	1	1	2	2	2	2	2	3	4	3	3	4
1	3	3	3	4	4	1	1	2	2	2	1	2	2	3	4	3	3
2	3	3	3	4	4	1	2	2	2	2	2	2	3	4	4	4	4
1	3	3	4	4	4	2	1	2	2	2	1	1	3	4	3	3	3
2	3	3	3	4	4	1	1	2	2	2	2	1	2	3	4	4	3
1	3	3	3	4	4	1	1	1	1	1	2	1	3	3	3	3	4
2	3	3	3	4	4	1	1	2	2	2	2	2	2	4	4	3	3
1	3	2	3	4	4	1	1	2	2	1	2	1	3	3	3	3	3
2	3	3	4	4	4	1	1	2	2	1	1	2	3	3	4	4	3
1	3	3	4	5	4	1	1	1	2	2	2	1	2	3	4	4	4

FENTANYL[µg]	COMPLICATIONS		
	NAUSEA	VOMITING	DROWSINESS
150	A	A	A
140	A	A	A
160	A	A	A
150	A	A	A
160	A	P	A
160	A	A	A
150	A	A	A
140	A	A	A
170	A	A	A
200	A	P	P
160	A	A	A
160	A	P	A
170	A	A	A
160	P	A	A
200	A	A	A
180	A	A	A
190	A	A	A
10	A	A	A
10	A	A	A
20	A	A	A
20	A	P	P
40	A	A	P
40	A	A	A
30	A	A	P
30	A	A	P
30	P	A	A
20	A	A	A
20	A	A	A
30	P	A	A
40	A	A	P
20	A	A	P
20	A	A	A
30	P	P	A
20	A	A	A
20	A	A	A
40	A	A	P
30	A	A	P
20	P	A	A
20	A	P	A
20	A	A	A
20	A	P	A
10	P	P	A
60	A	A	A
50	A	A	A
60	A	A	A
30	A	A	A
70	A	A	P
80	A	A	A
60	A	A	A
40	A	A	A
40	A	P	A
30	A	A	A
50	A	A	A
40	A	A	A
60	A	A	A
50	A	A	A
70	A	A	A
40	P	A	A
40	A	A	A
60	A	A	A
50	A	A	A
60	A	A	A
40	A	A	A
50	A	A	A
30	A	A	A
50	A	A	A
60	A	A	A